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Contents

Page

Some Clinical Aspects of Life at High Altitudes. ALBERTO HURTADO 247

Electrolyte Metabolism and Aldosterone Secretion in Benign and Malignant Hypertension. JOHN H. LARAGH, STANLEY ULICK, VLODZIMIERZ JANUSZEWICZ, WILLIAM G. KELLY and SEYMOUR LIEBERMAN 259

A Clinical Study of the Chronic Lung Disease due to Nonphotochromogenic Acid-Fast Bacilli. ALBERT G. LEWIS, JR., EUNICE M. LASCHÉ, ALLAN L. ARMSTRONG and FRANK P. DUNBAR 273

The Liver in Porphyria Cutanea Tarda. JAN WALDENSTRÖM and BIRGITTA HAEGER 286

The Occurrence of Intracellular Iron in Gaucher's Disease. MORTIMER LORBER ... 293

A Practical, Systematic Laboratory Approach to the Study of the Peripheral Circulation. HAROLD L. KARPMAN, J. HOWARD PAYNE and TRAVIS WINSOR 306

Experience with Punch Biopsy of Synovium in the Study of Joint Disease. GERALD P. RODNAN, EDUARDO J. YUÑIS and ROBERT S. TOTTEN 319

Electrocardiographic Changes Produced by Localized Hypothalamic Stimulations. S. J. WEINBERG and JOAQUIN M. FUSTER 332

Chlorothiazide and Hydrochlorothiazide: A Comparative Study of Their Hypotensive, Saluretic and Hyperuricemic Action. NEMAT O. BORHANI 342

Chromosome Abnormalities in Certain Diseases of Man. M. A. FERGUSON-SMITH and A. W. JOHNSTON 359

Carbohydrate Metabolism in Pentosuria. HOWARD H. HIATT 372

Case Reports:

Waldenström's Macroglobulinemia with Cryoglobulinemia. MARJORIE S. STERIDGE 380

Plasma Thromboplastin Component Deficiency in the Ehlers-Danlos Syndrome. RUBÉN LISKER, ARNOLDO NOGUERÓN and LUIS SÁNCHEZ-MEDAL 388

Pneumatosis Cystoides Intestinalis. JOSEPH P. WHITTLE 395

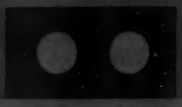
Intrathoracic Accessory Lobe of the Liver. S. A. KAUFMAN and IRVING M. MADOFF 403

Periodic Peritonitis, Onset Simultaneously with Menstruation. JULIUS SCHWARTZ 407

Editorial—Exclusion of Paternity 412

Reviews 420

Medical News IX

Just two tablets  *at bedtime*

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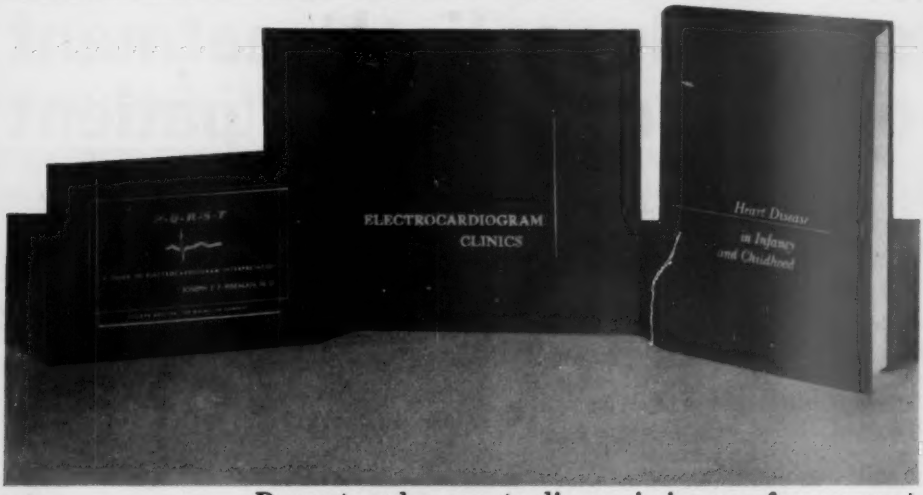

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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

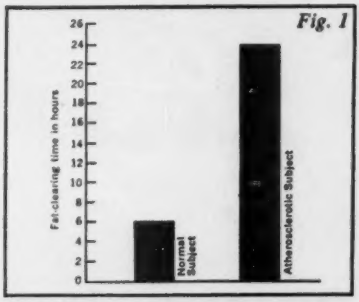
"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2*, the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

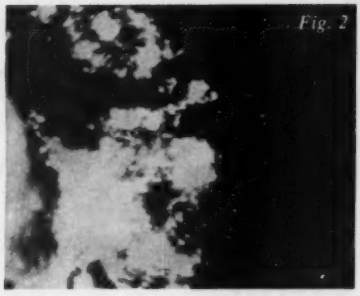
In *figure #3*, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

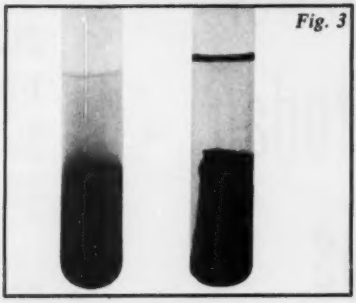
'Clarin', which is heparin in the form of a *sublingual tablet*, has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. 8. Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.







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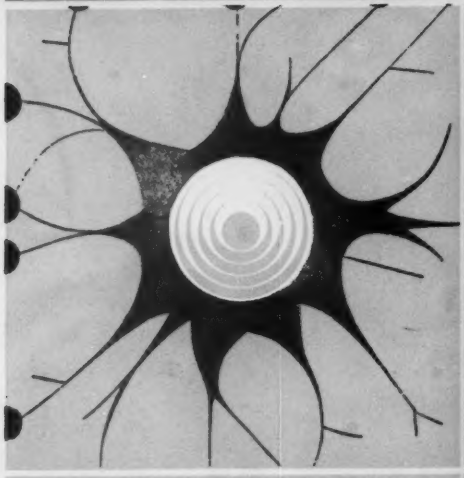

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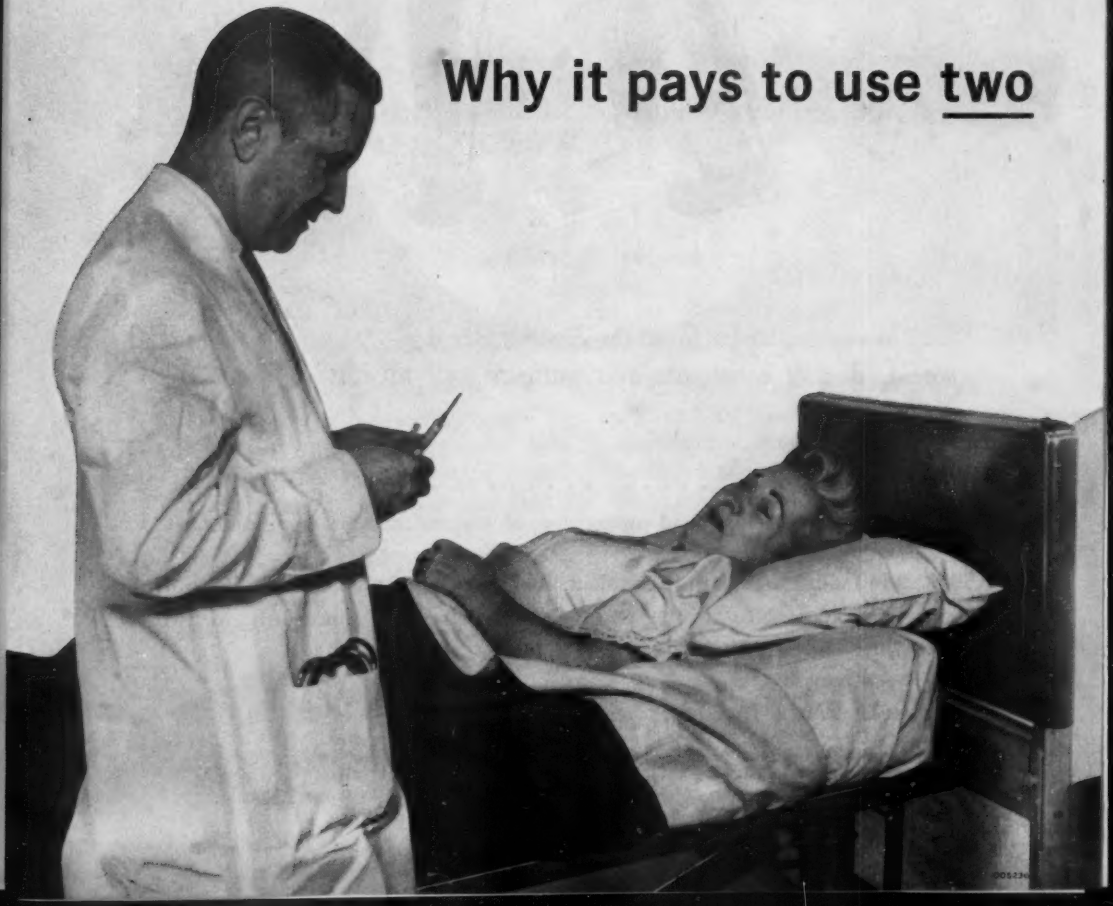

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(1) Williamson, P.: Practical Use of the Office Laboratory and X-Ray, Including the Electrocardiograph, St. Louis, C. V. Mosby Company, 1957, p. 41. (2) Free, A. H., and Fonner, D. E.: Studies With a Combination Test for Detection of Glucose and Protein, Abstract of 133rd Meeting, American Chemical Society, San Francisco, April 13-18, 1958, pp. 14c-15c.

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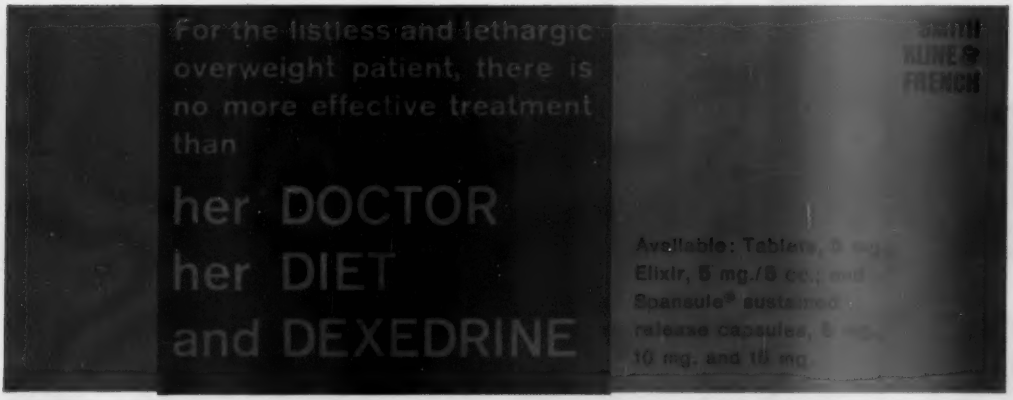
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1. Johnson, M.L., et al.: Am. J. Clin. Nutrition 4:37, 1956.
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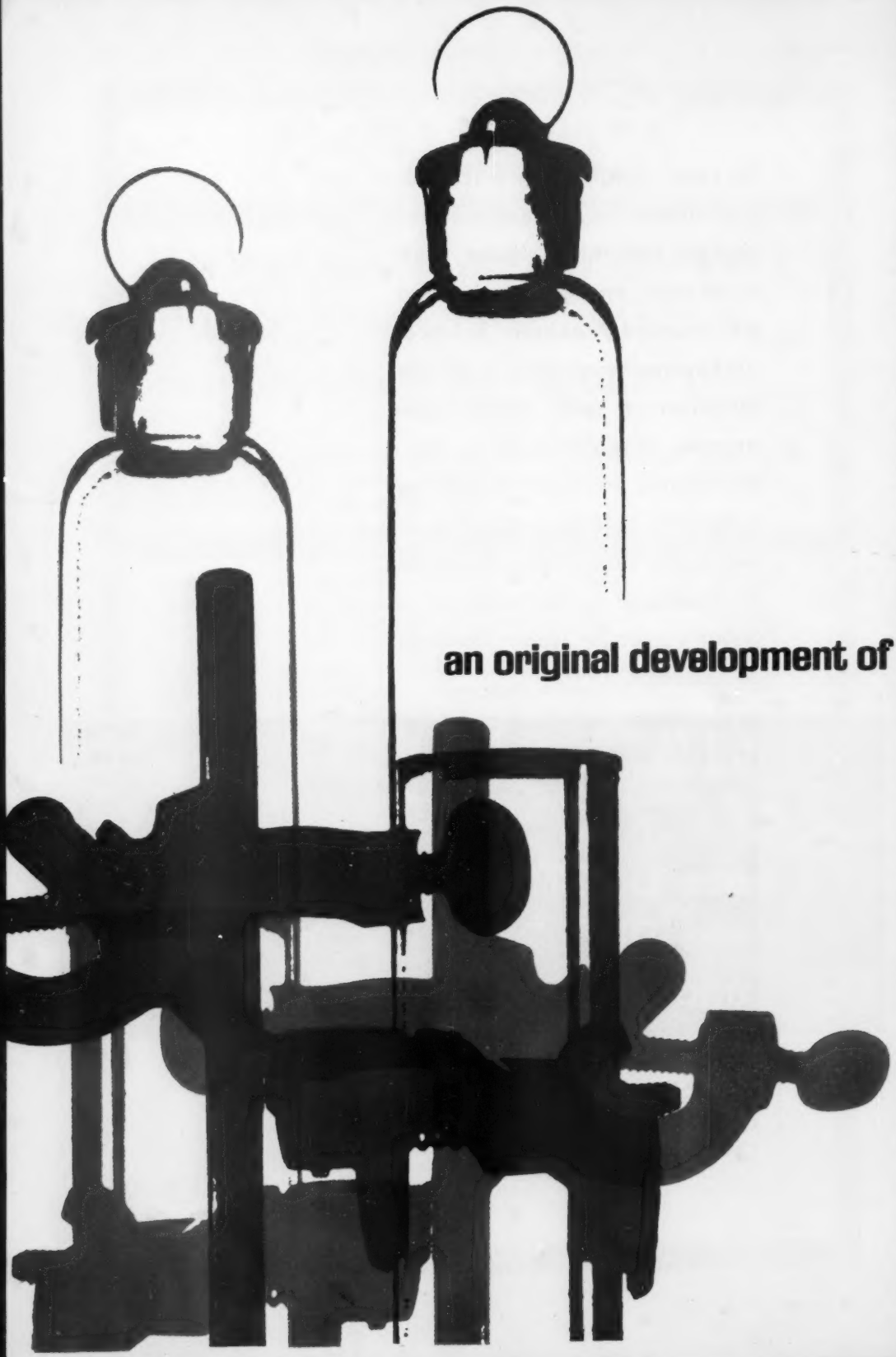

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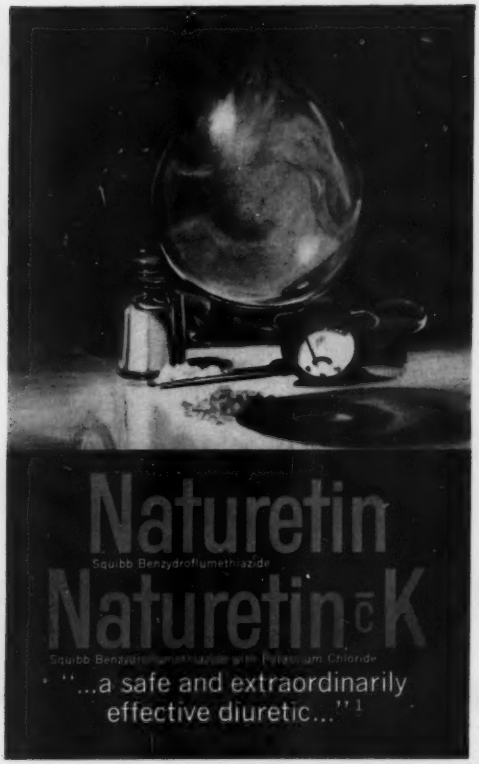

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Although Naturetin causes the least serum potassium depletion as compared with other diuretics, supplementary potassium chloride in Naturetin c̄ K provides added protection when treating hypokalemia-prone patients; in conditions where likelihood of electrolyte imbalance is increased or during extended periods of therapy.

Numerous clinical studies confirm the effectiveness[1-15] of Naturetin as a diuretic and antihypertensive — usually in dosages of 5 mg. per day.

■ the most potent diuretic, mg. for mg.—more than 100 times as potent as chlorothiazide ■ prolonged action — in excess of 18 hours ■ maintains its efficacy as a diuretic and antihypertensive even after prolonged or increased dosage use ■ convenient once-a-day dosage — more economical for patients ■ low toxicity — few side effects—low sodium diets not necessary ■ not contraindicated except in complete renal shutdown ■ *in hypertension*—significant lowering of the blood pressure. Naturetin may be used alone or with other antihypertensive drugs in lowered doses.

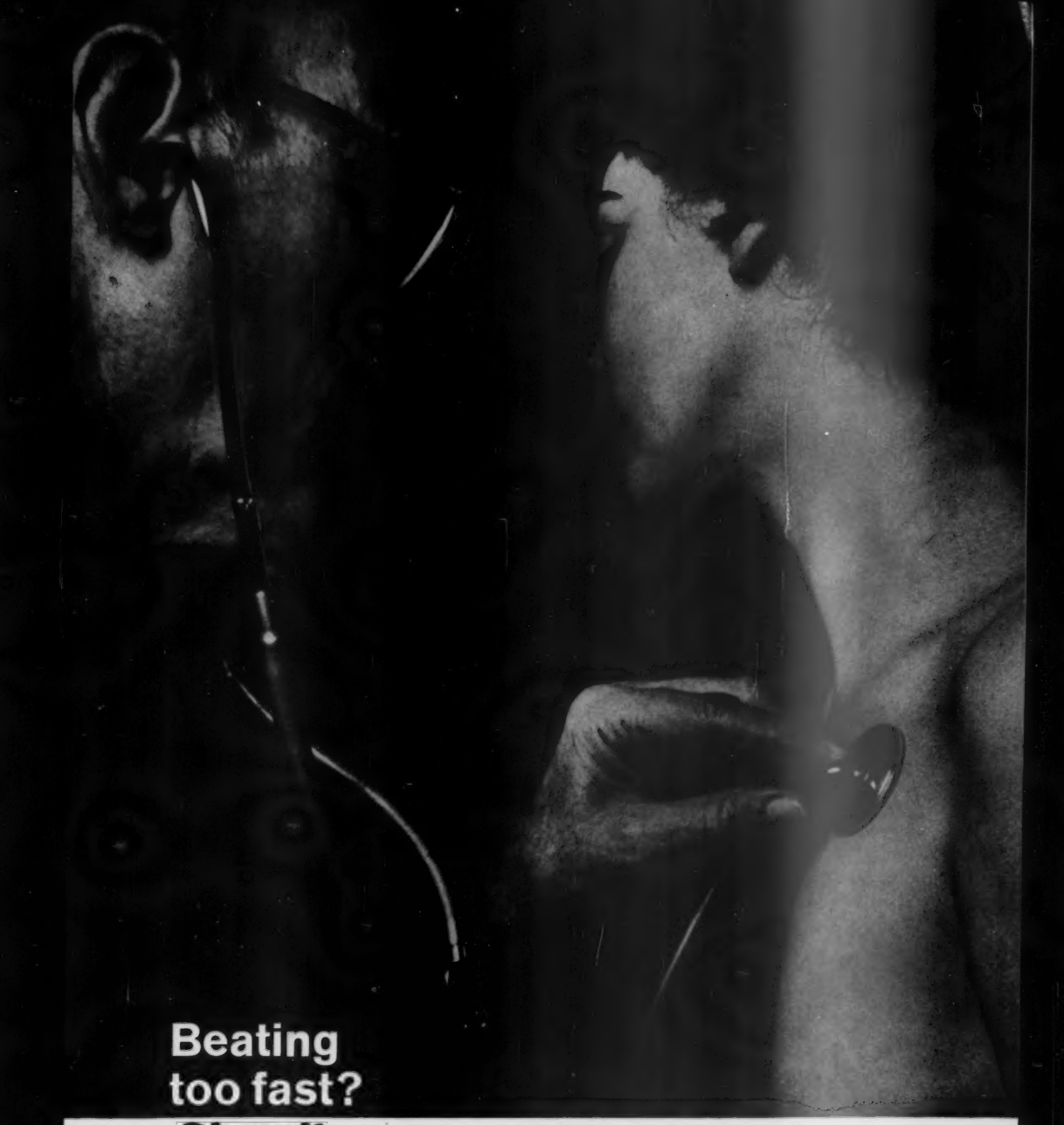
Supplied: Naturetin Tablets, 5 mg. (scored) and 2.5 mg. Naturetin c̄ K (5 c̄ 500) Tablets (capsule-shaped) containing 5 mg. benzydroflumethiazide and 500 mg. potassium chloride. Naturetin c̄ K (2.5 c̄ 500) Tablets (capsule-shaped) containing 2.5 mg. benzydroflumethiazide and 500 mg. potassium chloride.

SQUIBB

References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Stenberg, E. S., Jr.; Benedetti, A., and Forsham, P. H.: Op. cit. 5:46 (Feb.) 1960. 3. Fuchs, M.; Moyer, J. H., and Newman, B.E.: Op. cit. 5:55 (Feb.) 1960. 4. Marriott, H. J. L., and Schamroth, L.: Op. cit. 5:14 (Feb.) 1960. 5. Ira, G. H., Jr.; Shaw, D. M., and Bogdonoff, M. D.: North Carolina M. J. 21:19 (Jan.) 1960. 6. Cohen, B. M.: M. Times, to be published. 7. Breneman, G. M., and Keyes, J. W.: Henry Ford Hosp. M. Bull. 7:281 (Dec.) 1959. 8. Forsham, P. H.: Squibb Clin. Res. Notes 2:5 (Dec.) 1959. 9. Larson, E.: Op. cit. 2:10 (Dec.) 1959. 10. Kirkendall, W. M.: Op. cit. 2:11 (Dec.) 1959. 11. Yu, P. N.: Op. cit. 2:12 (Dec.) 1959. 12. Weiss, S.; Weiss, J., and Weiss, B.: Op. cit. 2:13 (Dec.) 1959. 13. Moser, M.: Op. cit. 2:13 (Dec.) 1959. 14. Kahn, A., and Greenblatt, L. J.: Op. cit. 2:15 (Dec.) 1959. 15. Grollman, A.: Monographs on Therapy 5:1 (Feb.) 1960.

'NATURETIN' IS A SQUIBB TRADEMARK.

Squibb Quality—the Priceless Ingredient



Beating too fast?

Slow it down with SERPASIL®

(reserpine CIBA)

Serpasil has proved effective as a heart-slowing agent in the following conditions: mitral disease; myocardial infarction; cardiac arrhythmias; neurocirculatory asthenia; thyroid toxicosis; excitement and effort syndromes; cardiac neurosis; congestive failure. Serpasil should be used with caution in patients receiving digitalis and quinidine. It is not indicated in cases of aortic insufficiency.

SUPPLIED: Tablets, 0.1 mg., 0.25 mg. (scored) and 1 mg. (scored). Complete information available on request.

CIBA

SUMMIT • NEW JERSEY

a new high-performance penicillin molecule

provides the physician with an added measure of assurance

provides the patient with an added measure of therapeutic effectiveness

TABLETS

DARCIL

Efficiently absorbed

Peak blood levels rapidly induced

Highest oral penicillin blood levels

Predictable blood levels

Highest urinary excretion

Lethal in vitro to many Staph. strains resistant to other penicillins

DARCIL (phenethicillin potassium) is *more rapidly* and *more completely* absorbed from the gastrointestinal tract than any other type of penicillin molecule. As a result, tissues are more likely to be supplied with adequate penicillin, despite individual patient-variation in the absorption of drugs. Blood concentrations of DARCIL directly reflect dosage levels, permitting adjustment of dosage to severity of infection.

A Century of Service to Medicine

Many strains of Staph. aureus susceptible

Morigi *et al.*[1] administered phenethicillin potassium to 47 patients with a variety of bacterial infections caused by penicillin-susceptible organisms. Twenty strains of *Staph. aureus* were isolated from pre-therapy cultures; 19 were highly susceptible to phenethicillin potassium *in vitro:* one was resistant. Of 47 patients treated, 38 were cured; 6 improved, and 3 were unresponsive.

Prompt regressoin of symptoms

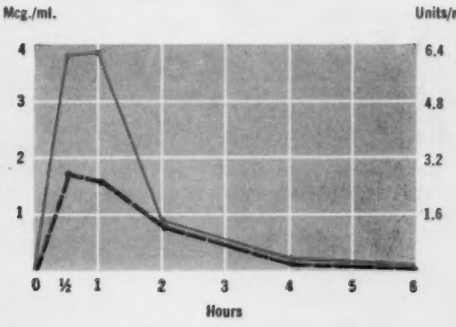
Cronk *et al.*[2] report prompt regression of symptoms and disease in 38 patients with diseases caused by penicillin-susceptible organisms. *The authors conclude that further experience will undoubtedly demonstrate the antibiotic to be highly efficacious in all infections caused by susceptible organisms.*

References: 1. Morigi, E.M.E., *et al.:* Antibiotics Annual 1959-1960 Antibiotica Inc., New York, N.Y. pp. 127-132. 2. Cronk, G.A., *et al.: Ibid.* pp. 133-145. 3. Wright, W.: Reported in Morigi, E.M.E., *et al.: Ibid.* 127-132.

Average penicillin serum concentrations[3] following a single 250-mg. dose

———— phenethicillin potassium

– – – – potassium penicillin V



Average penicillin urine concentrations[1] following a single 250-mg. dose

	0-6 Hrs.	6-12 Hrs.	24 Hrs.
[illegible]	[illegible]	[illegible]	[illegible]
potassium penicillin V	18.2%	0.2%	0%

TABLETS

DARCIL*

Penicillin-152 Potassium

phenethicillin potassium, Wyeth

DARCIL is a new penicillin molecule, designated chemically as potassium α-phenoxyethyl penicillin. It is remarkably stable in acid solutions; is lethal in vitro to clinical isolates of certain strains of staphylococci resistant to other penicillins; has a lower CD_{50} (median curative dose) against certain organisms than the natural penicillins; and is efficiently absorbed from the gastrointestinal tract, yielding early high penicillin serum levels and urine excretion levels substantially higher than those observed following equivalent oral dosages of penicillin G or V.

DARCIL is active against streptococci (Groups A, B, C, and D), Diplococcus pneumoniae, Neisseria and Staphylococcus aureus, including some strains of that organism which are resistant to other penicillins. It is bactericidal in serum concentrations obtainable on oral administration. As is the case with other penicillins, bacterial resistance develops slowly.

Indications

DARCIL is recommended in the treatment of the following bacterial infections due to penicillin-susceptible organisms:

Respiratory Tract Infections: acute pharyngitis, septic sore throat, tonsillitis, otitis media, laryngitis, cervical adenitis, bronchitis and lobar or bronchopneumonia.

Skin; Soft Tissue and Surgical Infections: erysipelas, cellulitis, lymphangitis, wound infections and pyodermia.

Urinary Tract Infections: gonorrhea, acute and chronic cystitis, pyelonephritis and prostatitis.

Other Infections: scarlet fever and puerperal sepsis.

The clinical utility of DARCIL in the treatment of syphilis, endocarditis, or meningitis has not been established.

Dosage

Recommended Dosage: 125 mg. (200,000 units) or 250 mg. (400,000 units) three times daily depending on the severity of the infection. Larger doses of 500 mg. (800,000 units) three times daily or 250 mg. every four hours may be used for more severe infections.

Beta-hemolytic streptococcal infections should be treated for at least ten days to prevent the development of acute rheumatic fever.

Precautions

Allergic reactions to oral penicillin, although rare, are more likely to occur in patients with histories of hay fever, asthma, and those who have previously reacted adversely to penicillin. If the use of penicillin in such patients is imperative and reactions occur, the physician should have available resuscitative drugs such as epinephrine, antihistamines, aminophylline, etc., for intravenous administration, and discontinue further use. Administration of oral penicillin, in rare instances, may provoke acute anaphylaxis, particularly in penicillin-sensitive individuals.

The use of antibiotics occasionally results in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Loose stools have been reported occasionally. Other signs of toxicity are rare.

Supplied

Tablets, scored; each containing 250 mg. (400,000 units) phenethicillin potassium; vials of 36. *Trademark

Wyeth Laboratories Philadelphia 1, Pa.

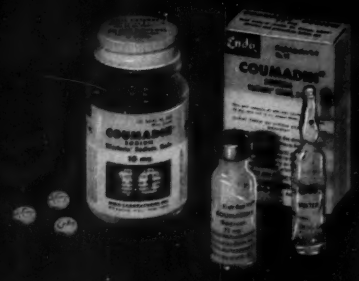
COUMADIN

the proven anticoagulant

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE*

Over 60 published papers since 1953

Over ~~90,000,000~~ doses administered to date



COUMADIN is the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.[1]

Full range of oral and parenteral dosage forms—COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2-cc. ampul Water for Injection; one vial, 75 mg., and one 3-cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patient, 20-30 mg.

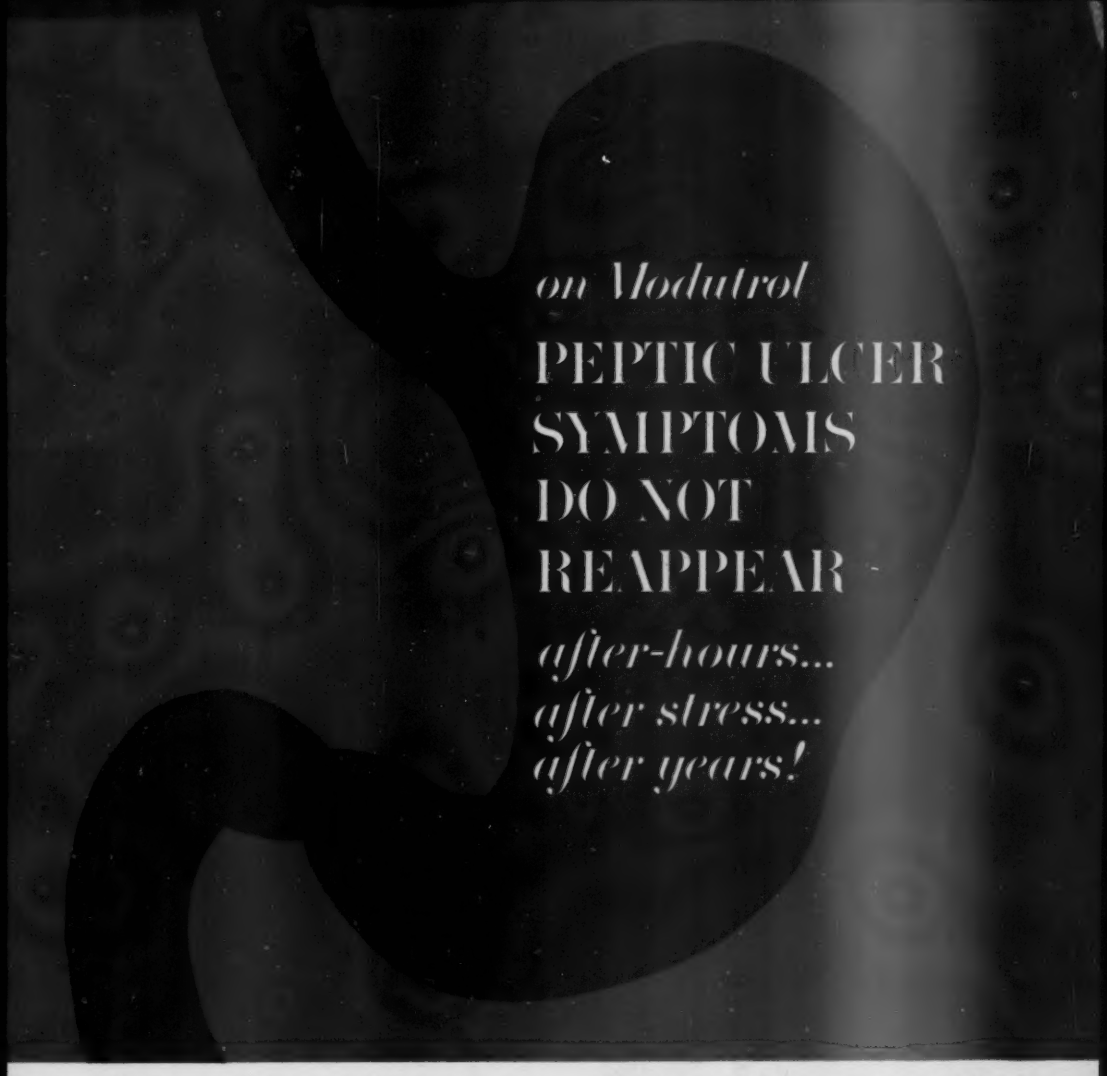
Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

1. Boer, S., et al.: J.A.M.A. 157:701, June 2, 1955.
2. Mayer, K. (4): Diseases of the Chest, Chicago, Yr. Bk. Pub., Mar., 1955, p. 11.

Endo

Complete Information and Reprints on Request
ENDO LABORATORIES, Richmond Hill 18, New York

*Manufactured under license from the Wisconsin Alumni Research Foundation



Modutrol allows complete and *lasting freedom* from symptoms—without dietary restrictions. Of all agents tested, only Modutrol achieved the three rigid objectives for success in peptic ulcer therapy: relief of symptoms, healing of ulcer and prevention of recurrences or complications. Moreover, Modutrol met these criteria in over 96 per cent of all patients tested.[1]

Psychophysiologic Medication To Combat A "Psychovisceral Process"

Therapeutic efficacy of Modutrol is enhanced by its psycho-active component, Sycotrol—proved clinically to be not only more effective than either sedatives or tranquilizers, but ideally suited for ambulatory patients because they do not experience commonly encountered side effects of depression and habituation. Sycotrol, a psychotropic agent with antiphobic properties, acts against fears and anxieties that find outlets in visceral manifestations. Modutrol combines the psycho-active agent with preferred antacid and anticholinergic therapy to provide total management of the disorder.

FORMULA: Each Modutrol tablet contains: Sycotrol (pipethanate hydrochloride) 2 mg., scopolamine methylnitrate 1 mg., magnesium hydroxide 200 mg., aluminum hydroxide 200 mg.

DOSAGE: One tablet 3 or 4 times daily.

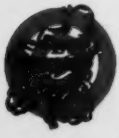
SUPPLIED: Bottles of 50 and 100 tablets.

CONTRAINDICATIONS: Contraindicated in glaucoma because of its anticholinergic components.

1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

Also available: Sycotrol tablets 2 mg. Bottles of 100 tablets.

R&C **REED & CARNRICK** *Kenilworth, New Jersey*



Psycho-physiologic Management

MODUTROL®

When the Target Organ of Fear-anxieties is the G.I. Tract and Peptic Ulcer Results.

Therapeutic vitamins in the "therapeutic" jar

All alcoholics, whether cirrhotic or not, should receive high levels of B-complex and C vitamins[1] as provided by STRESSCAPS, since the reversal of nutritional failure and its resultant morbidity depends largely on the water-soluble vitamins. Therapeutically important, the decorative jar serves as a constant dosage reminder for the alcoholic patient . . . who frequently is antagonistic to rehabilitation.

Each capsule contains: Thiamine Mononitrate (B_1) 10 mg., Riboflavin (B_2) 10 mg., Niacinamide 100 mg., Ascorbic Acid (C) 300 mg., Pyridoxine HCl (B_6) 2 mg., Vitamin B_{12} 4 mcgm., Folic Acid 1.5 mg., Calcium Pantothenate 20 mg., Vitamin K (Menadione) 2 mg. Average dose: 1-2 capsules daily.

1. Davidson, C. S.: Am. J. Med. 25:690 (Nov.) 1958.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.

STRESSCAPS®

Stress Formula Vitamins Lederle

IN ALCOHOLISM

solves problem...

SAVES FLAVOR!

ADOLPH'S is the salt substitute that solves the dieter's problem by saving the flavor! Looks, sprinkles and seasons like salt — and at the same time helps to provide supplemental potassium needed in low-sodium diets. At grocery stores everywhere. For free shaker samples write Adolph's Ltd., Burbank, California.

Another fine product from Adolph's Diet Kitchens

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are your Hypertensives bothered by

NASAL CONGESTION?

Of 403 Hypertensive and Anxiety Patients Treated with Harmonyl, only 12—2.7%—Reported Nasal Congestion*

switch your working hypertensives to

Harmonyl®

(Deserpidine, Abbott)

ABBOTT

***See page 31 for footnotes and dosages.*

Helps you take the misery out of menopause

as hormones alone often don't do

Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

Milprem®

(Miltown® plus natural estrogens)

CMP-1306

WALLACE LABORATORIES/*New Brunswick, N. J.*

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PLEASE NOTIFY US OF ANY CHANGE OF ADDRESS AND FORWARD TO:

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NAME .....
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OLD ADDRESS:	**NEW ADDRESS:**
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City and Zone	City and Zone .....
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REMARKS .....

are your Hypertensives troubled with

LETHARGY?

*Of 403 Hypertensive and Mixed Anxiety Patients Treated with Harmonyl, only 13—2.9%—Reported Lethargy**

switch your working Hypertensives to

Harmonyl®
(Deserpidine, Abbott)

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**See page 31 for footnotes and dosages.*

"The larger the therapeutic range...the more desirable the preparation... [GITALIGIN]...possesses a greater range."*

WIDER SAFETY MARGIN

GITALIGIN®†

"...possesses a greater range."*

GITALIGIN provides a maximum degree of control in cardiac therapy by reason of these distinctive clinical features:**

WIDER SAFETY MARGIN

GREATER THERAPEUTIC RANGE

FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF

It's easy to transfer patients to GITALIGIN —*without interruption*—

0.5 mg. Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.1 mg. digitoxin, and 0.5 mg. digoxin.

Supplied: 0.5 mg. scored tablets—in bottles of 30 and 100.

*Batterman, R. C.: Observations on the Clinical Use of Digitalis, in Diamond, E. G.: Digitalis, Springfield, Charles C Thomas, 1957.

**Bibliography available on request.

†White's brand of amorphous gitalin.

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clinically proved
oral penicillin therapy
that costs your
patients less

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Squibb Penicillin G Potassium

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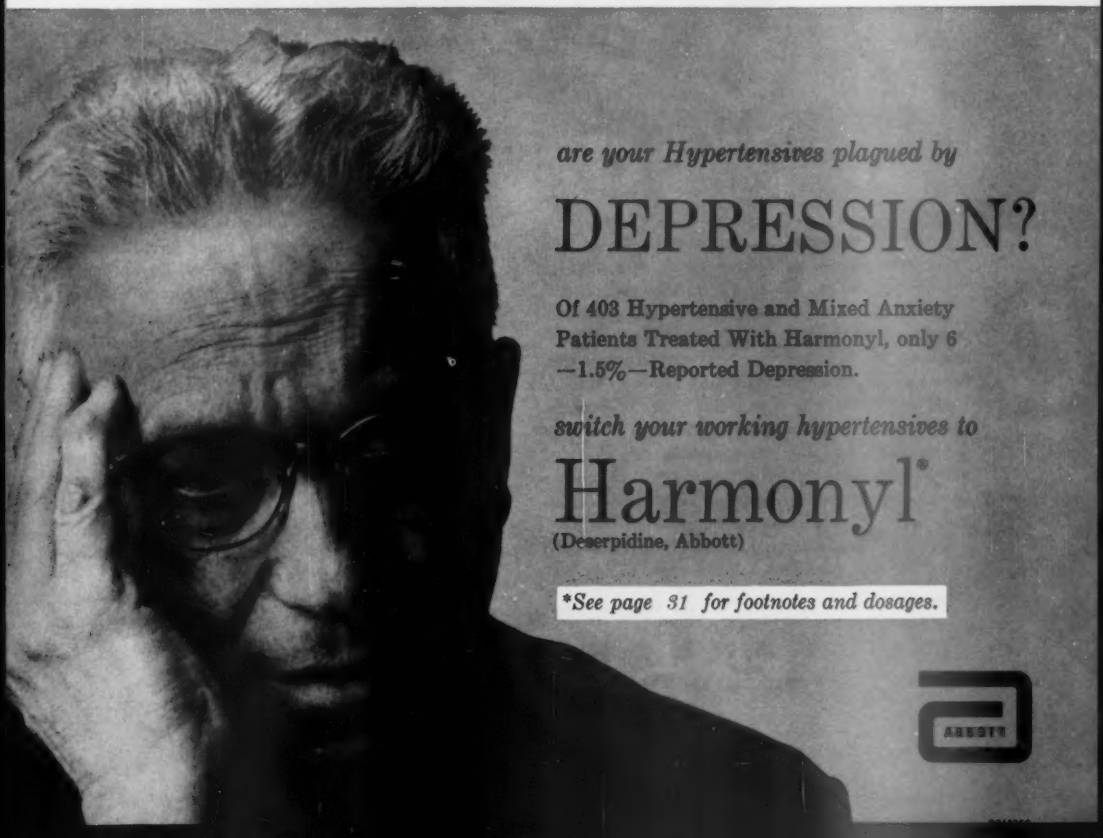


are your Hypertensives plagued by

DEPRESSION?

Of 403 Hypertensive and Mixed Anxiety Patients Treated With Harmonyl, only 6 —1.5%—Reported Depression.

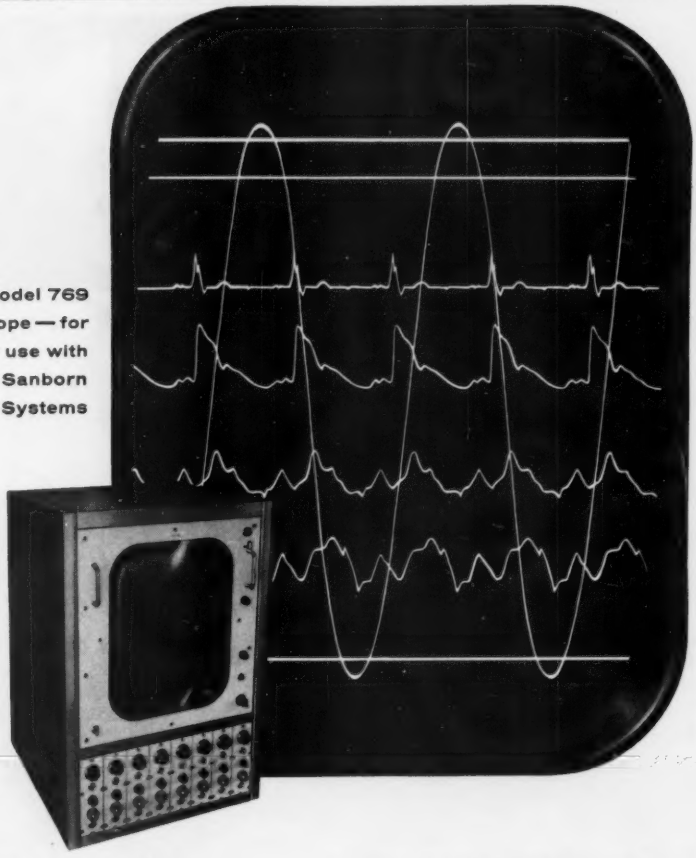
switch your working hypertensives to

Harmonyl®

(Deserpidine, Abbott)

*See page 31 for footnotes and dosages.

ABBOTT



Sanborn Model 769 Viso-Scope — for monitor use with existing Sanborn Recording Systems

8 EVENTS AT ONCE . . . ON A 17 INCH SCREEN

THE vertically mounted 17″ screen provides ample space for up to 8 clear, long-persistance traces to be shown simultaneously on the Sanborn Model 769 Viso-Scope. Individual plug-in gating amplifiers in the 769 perform the function of an electronic switch — one amplifier for each signal to be shown on the 'scope — the signals being derived by direct connection of the 769 to existing Sanborn Recording Systems such as Model 60 Twin-Viso, Models 64, 77M, 150M and 350M Poly-Visos, and 550M Poly-Beam.

Automatic or manual trace sweep speeds of 2, 4 and 8 seconds (5, 2.5, and 1.25 inches/sec) are provided and an additional manual sweep speed of 25 seconds is included for use when slowly changing waveforms such as dye dilution curves are studied.

Controls permit sensitivity ranges from 5″/volt to ⅛″ per volt, positioning of each signal at any level on the screen, and vector loop presentation. A Polaroid filter is used to minimize interference from room lighting, and provision is made for tilting the 'scope unit forward (up to 20 degrees) for optimum viewing ease. Front and rear input connections are available. With suitable cabling, several 769 units can be connected together for master slave operation.

The Model 769 Viso-Scope — scheduled for delivery starting in September — is the first of a group of Sanborn "760" Monitor Units (including low voltage preamplifiers) soon to be made available for use in Hospital Operating Rooms, Recovery Rooms and Intensive Care Units, and by Catheterization Units and Teaching Groups.

For complete details, contact your nearest Sanborn Branch Office or Service Agency, or write the Inquiry Director at the Main Office in Waltham.

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MEDICAL DIVISION, 175 WYMAN STREET, WALTHAM 54, MASS.

Lethargy in Drug Treatment of Hypertension

Of 446 Hypertensive and Mixed Anxiety Patients Treated With Harmonyl®, only 13—2.9%—Reported Lethargy

Presented are notes from four clinical studies. Harmonyl was used as sole agent of therapy by 446 mixed hypertensives, and patients with mild functional/psychiatric disorders. Only thirteen reported lethargy (9 mild) with therapy—an incidence of 2.8%.

Study #1. Two hundred and eighty-three patients treated in private practice, at hospital outpatient clinics, and in office psychiatric practice. Average initial dosage of Harmonyl was 0.1 mg. to 0.25 mg. three or four times daily. Maximum dose was 6 mg. daily. Nine reports of lethargy (all mild).

Study #2. Eighty patients with benign essential hypertension were studied via "double-blind" method. Mean daily dosage of Harmonyl was 0.25 mg., with a minimum dosage of 0.1 mg. and a maximum of 0.5 mg. daily. One report of lethargy.

Study #3. Forty patients with hypertension and anxiety neurosis . . . from mild to moderately severe. Half of group had received other antihypertensive agents at one time or another; these were discontinued before and throughout the study. Usual dosage of Harmonyl was 0.1 mg. three times daily after meals. Sometimes an additional dose was taken at bedtime. Two reports of lethargy.

Study #4. Forty-three patients with tension and anxiety problems typical of general practice. Studied by "double-blind" method. Dosage was 0.25 mg. Harmonyl three times daily. One report of lethargy.

Generally speaking, these investigators feel Harmonyl therapy produces the desired results with fewer and less severe side-effects than are sometimes seen with other agents. There is less disruption of the patient's ability to live and work normally, and there is seldom any need to curtail or discontinue Harmonyl treatment because of side reactions.

1. Billow, B.W. et al, The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, 35:415, April, 1959.
3. Rawls, W.B. and Evans, W.L. Jr., Clinical Experiences with Deserpidine in the Management of Hypertension and Anxiety Neurosis, N.Y. J. Med., 59:1774, May, 1959.
4 Frohman, I.P., Tranquilizers in General Practice and Clinical Evaluation of Deserpidine, An Alkaloid of Rauwolfia Canescens, Med. Ann. District of Columbia, 27:641, December, 1958.

switch your working hypertensives to

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(Deserpidine, Abbott)

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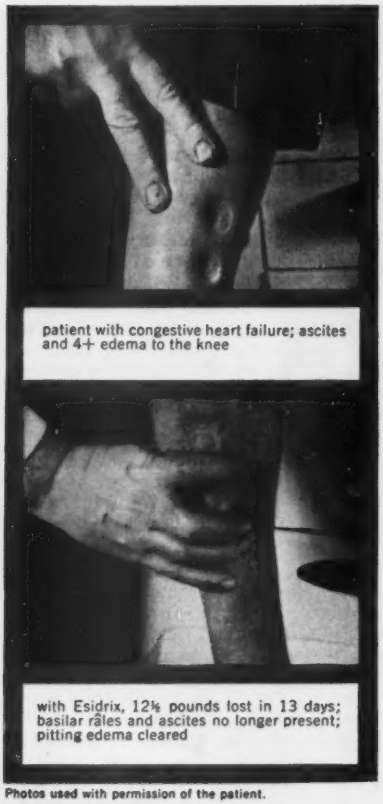


patient with congestive heart failure; ascites and 4+ edema to the knee

with Esidrix, 12½ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema cleared

Photos used with permission of the patient.

benefits in edema, benefits in hypertension plus added potassium protection

NEW ESIDRIX-K T.M.

New ESIDRIX-K provides all the oral diuretic-antihypertensive advantages of ESIDRIX, plus a properly proportioned potassium supplement. ESIDRIX produces marked excretion of salt and water in edematous patients, and in many hypertensive patients significantly reduces blood pressure, alone or with other antihypertensive drugs. Potassium excretion is minimal, and the built-in K supplement further helps eliminate problems due to potassium loss. Three ESIDRIX-K tablets provide potassium equivalent to one quart of fresh orange juice; ESIDRIX-K is coated to prevent gastric irritation.

Complete information sent on request.

Supplied: Esidrix-K Tablets (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored).

Esidrix-K is especially indicated for patients in whom even moderate potassium loss can cause complications, or those whose condition predisposes to hypokalemia. Among candidates for Esidrix-K are patients taking digitalis for congestive heart failure, those with renal or liver disease, those under long-term treatment, and those on salt-restricted diets.

C-I-B-A
SUMMIT, NEW JERSEY

ESIDRIX® (hydrochlorothiazide CIBA)

2/3941MR

how does Mellaril differ from other potent tranquilizers?

Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization,
relieves anxiety, tension, nervousness,

but is virtually free of such toxic effects as

jaundice
Parkinsonism
blood dyscrasia
dermatitis

SANDOZ

greater specificity of tranquilizing action results in fewer side effects

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such "diffuse" effects as antiemetic action.

Mellaril

THIORIDAZINE HCl

specific, effective tranquilizer

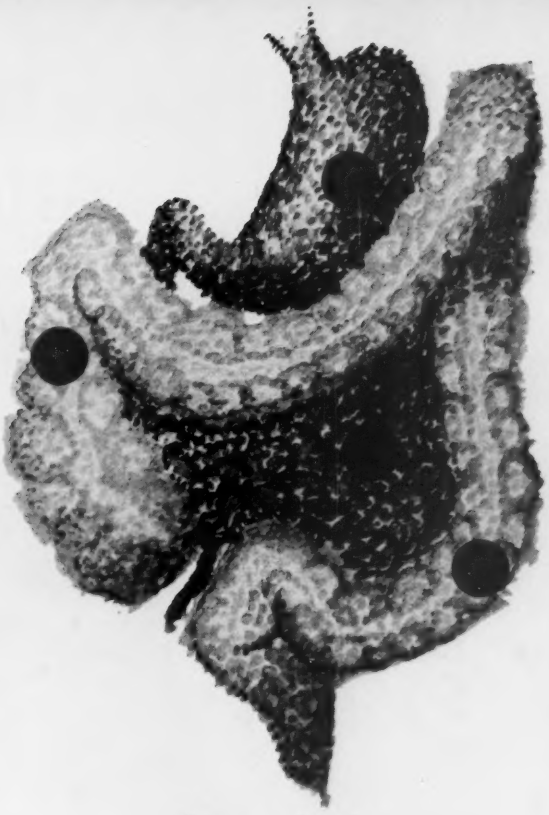
"The most striking aspect of thioridazine [MELLARIL] therapy is the poverty of side-effects."

"In conclusion it may be said that thioridazine is at least as effective in relieving psychiatric illness as other drugs of its class. On a milligram for milligram basis it has the same order of potency as chlorpromazine. In its low incidence of side-effects and toxicity, it is superior to all other tranquilizing drugs tested. For this reason it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication with other drugs because of dizziness, sleepiness, increased tension, or Parkinsonism."[a]

Supply: MELLARIL Tablets, 10 mg., 25 mg., 100 mg.

SANDOZ

[a]Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders, J.A.M.A. 170:1283, July 11, 1959.



for peptic ulcer...
for gastrointestinal disorders, specify

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COMPLETE THERAPEUTIC NUTRIMENT

to help restore and maintain good nutrition

in peptic ulcer

Sustagen "...systematically enhances healing of the ulcer and restoration of the patient to a state of optimal nutrition."[1]

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"...high protein, high carbohydrate, high caloric, low residue diet"[2] imperative. Sustagen provides this diet.

provides all essential nutrients

Sustagen may be used as the sole source of food or to fortify the diet—helps build and repair tissue, restore nitrogen balance, enhance rehabilitation.

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Palatable,[3] easy to take in beverage form—just one glass provides 390 calories and 23.5 Gm. protein. In tube feeding Sustagen alone provides complete nutrition. Mixes and flows readily. Bland, low in bulk, low in fiber, it is well tolerated—easy to use, easy to take.

References:

(1) Winkelstein, A.: Am. J. Gastroenterol. *27*:45-52 (Jan.) 1957. (2) Brown, C. H.: Am. Pract. & Digest Treat. *9*:405-411 (March) 1958. (3) Winkelstein, A., and Schweiger, E.: J.A.M.A. *160*:1111-1113 (March 31) 1956.

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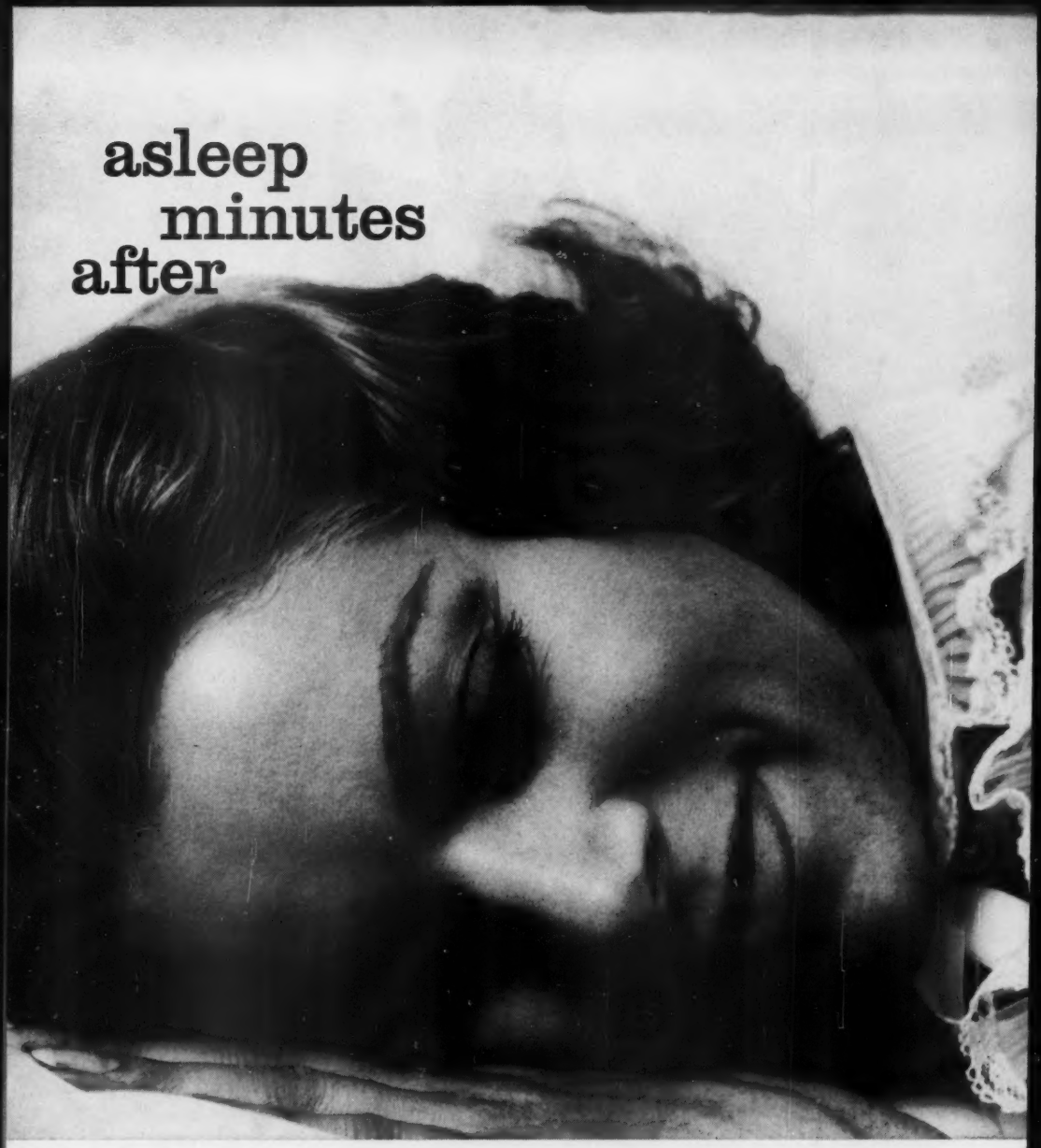

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"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., **59**:1769, (May 1) 1959.

in hypertension

". . . our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, **3**:199, (Feb.) 1959.

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in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.

in renal edema

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

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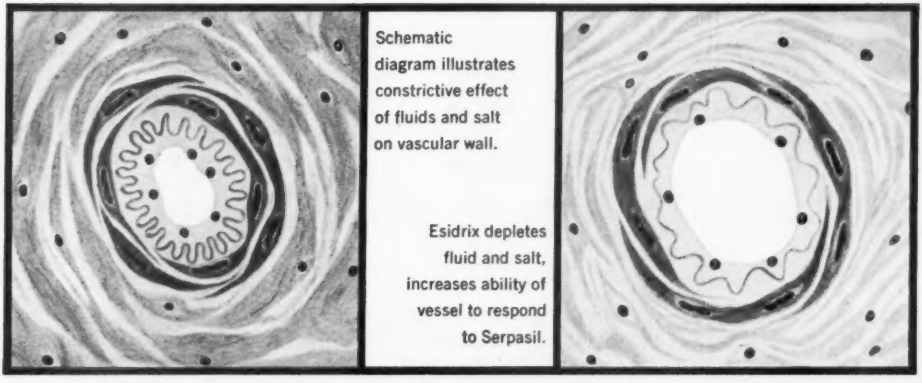
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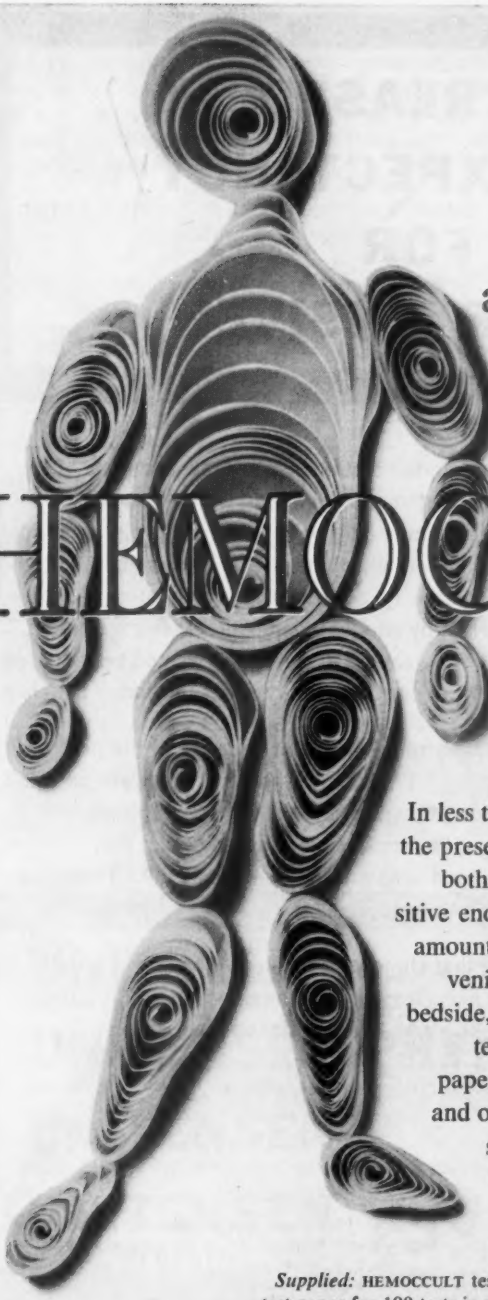

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INCREASED LIFE EXPECTANCY FOR HYPERTENSIVES

"Life expectancy seems to be the one criterion that is most reliable and least questioned as a method of evaluating treatment for patients with elevated blood pressure."[1] "It is evident that effective therapy of hypertension will prolong the life of the patient by preventing the dreaded complications of this disease in the brain, the heart and the kidneys." "There is no doubt of the prolongation of life in group 3 and 4 (Keith-Wagener-Barker) by adequate antihypertensive treatment. Some authorities report a 50 per cent, five year survival ratio for treated patients with malignant hypertension as against a 1 per cent survival ratio for untreated patients."[2]

Evaluation based on life expectancy is extremely difficult because of the peril of maintaining an untreated control group.[1] The doctor, however, can evaluate the symptoms related to the elevated blood pressure. . . . We know that retinopathy may improve, the heart may be reduced in size, the electrocardiogram may improve and in favorable cases the blood urea nitrogen level may fall.[2] These are reasonably objective criteria on which to base one's evaluation of treatment.[1]

On the succeeding page is evidence that Unitensen included in any therapeutic regimen may improve the results in hypertension as measured by a regression of objective clinical changes in a substantial proportion of the patients treated.

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Unlike diuretics or ganglionic blocking agents, Unitensen lowers blood pressure through widespread vasorelaxation. Normal vasomotor responses are not altered, and there is no venous pooling with resulting postural hypotension.[3-5] Through alleviation of cerebral vasospasm, Unitensen promotes cerebral blood flow and oxygen utilization.[6-9] Furthermore, Unitensen increases cardiac efficiency, improves renal function and tends to arrest the progress of vascular damage.[3, 4, 10]

Progress of Objective and Subjective Symptoms in Grades III and IV Hypertension Following Treatment with Unitensen and Unitensen-R

Observations in Patients* Treated up to 2 Years — **Observations in Patients* Treated up to 3½ Years**

The Course of Subjective Symptoms

Symptom	Number**	Improved	% Improved	Number**	Improved	% Improved
Headache	27	21	77.7	43	38	88.0
Palpitation	20	13	65.0	29	19	65.5
Angina	15	9	60.0	21	16	76.0
Dyspnea	17	8	47.0	27	14	51.0

Objective Changes Following Treatment

Finding	Number**	Improved	% Improved	Number**	Improved	% Improved
Funduscopic Changes	41	24	58.5	59	38	66.0
Enlarged Heart	20	13	65.0	35	23	65.7
Abnormal ECG	37	10	27.0	45	25	55.5
Proteinuria	31	12	38.7	43	27	62.7
Nitrogen Retention	17	6	35.2	28	10	35.7

Left hand charts from Clinical Exhibit "The Ambulatory Patient with Hypertension" presented AMA Convention, San Francisco, June 22-27, 1958, by B. M. Cohen, M.D.

Right hand charts include patients previously reported who had been continuously maintained on Unitensen and Unitensen-R, plus additional patients later added to the study. From Clinical Exhibit "The Office Diagnosis and Treatment of the Patient with Hypertension" presented American Academy of General Practice, Indianapolis, March 18-19, 1959, by B. M. Cohen, M.D.

*All patients in this study were initially classified as Smithwick Grades III and IV.

**Expressed as the number of patients exhibiting the symptom recorded.

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Each tablet contains: Cryptenamine (tannates) 2.0 mg.

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Each tablet contains: Cryptenamine (tannates) 1.0 mg., Phenobarbital 15 mg.

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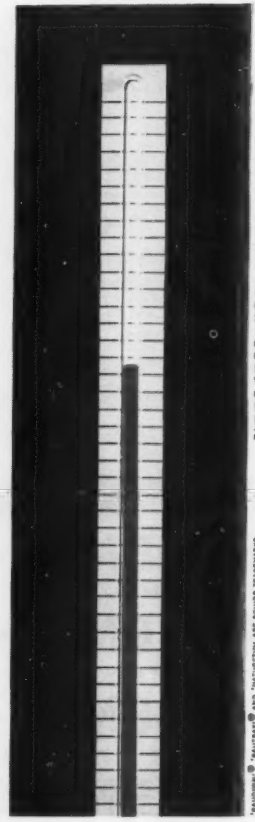
New Rautrax-N results in prompt lowering of blood pressure.[1] Rautrax-N, a new and carefully developed antihypertensive-diuretic preparation, provides improved therapeutic action[1] plus enhanced diuretic safety for all degrees of essential hypertension. A combination of Raudixin and Naturetin, Rautrax-N facilitates the management of hypertension when rauwolfia alone proves inadequate, or when prolonged treatment, with or without associated edema, is indicated.

Naturetin, the diuretic of choice, also possesses marked antihypertensive properties, thus complementing the known antihypertensive action of Raudixin. In this way a lower dose of each component in Rautrax-N controls hypertension effectively with few side effects and greater margin of safety.[1-16]



Other advantages are a balanced electrolyte pattern[1-16] and the maintenance of a favorable urinary sodium-potassium excretion ratio.[2-16] Clinical studies[1-5] have shown that the diuretic component of Rautrax-N—Naturetin—has only a slight effect on serum potassium. The supplemental potassium chloride provides additional protection against potassium depletion which may occur during long term therapy.

Rautrax-N may be used alone or in conjunction with other antihypertensive drugs, such as ganglionic blocking agents, veratrum or hydralazine, when such regimens are needed in the occasionally difficult patient.

Supply: Rautrax-N—capsule-shaped tablets providing 50 mg. Raudixin (Squibb Rauwolfia Serpentina Whole Root) and 4 mg. Naturetin (Squibb Benzydroflumethiazide), with 400 mg. potassium chloride.

Dosage: Initially-1 to 4 tablets daily after meals. Maintenance-1 or 2 tablets daily after meals; maintenance dosage may range from 1 to 4 tablets daily. For complete instructions and precautions see package insert. Literature available on request.

References: 1. Reports to the Squibb Institute, 1960. 2. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 3. Stenberg, E. S., Jr.; Benedetti, A., and Forsham, P. H.: Op. cit. 5:46 (Feb.) 1960. 4. Fuchs, M.; Moyer, J. H., and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 5. Marriott, H. J. L., and Schamroth, L.: Op. cit. 5:14 (Feb.) 1960. 6. Ira, G. H., Jr.; Shaw, D. M., and Bogdonoff, M. D.: North Carolina M. J. 21:19 (Jan.) 1960. 7. Cohen, B. M.: M. Times, to be published. 8. Breneman, G. M. and Keyes, J. W.: Henry Ford Hosp. M. Bull. 7:281 (Dec.) 1959. 9. Forsham, P. H.: Squibb Clin. Res. Notes 2:5 (Dec.) 1959. 10. Larson, E.: Op. cit. 2:10 (Dec.) 1959. 11. Kirkendall, W. M.: Op. cit. 2:11 (Dec.) 1959. 12. Yu, P. N.: Op. cit. 2:12 (Dec.) 1959. 13. Weiss, S.; Weiss, J., and Weiss, B.: Op. cit. 2:13 (Dec.) 1959. 14. Moser, M.: Op. cit. 2:13 (Dec.) 1959. 15. Kahn, A., and Grenblatt, I. J.: Op. cit. 2:15 (Dec.) 1959. 16. Grollman, A.: Monographs on Therapy 5:1 (Feb.) 1960.

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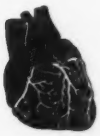

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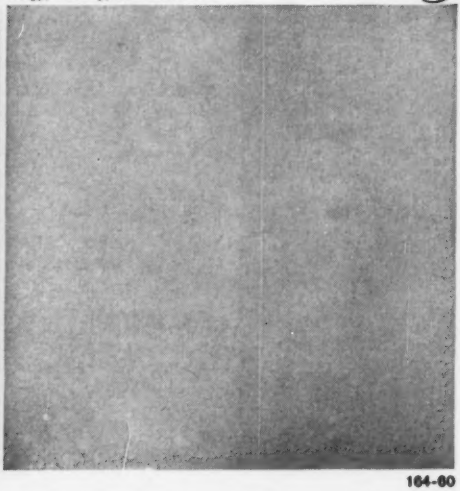

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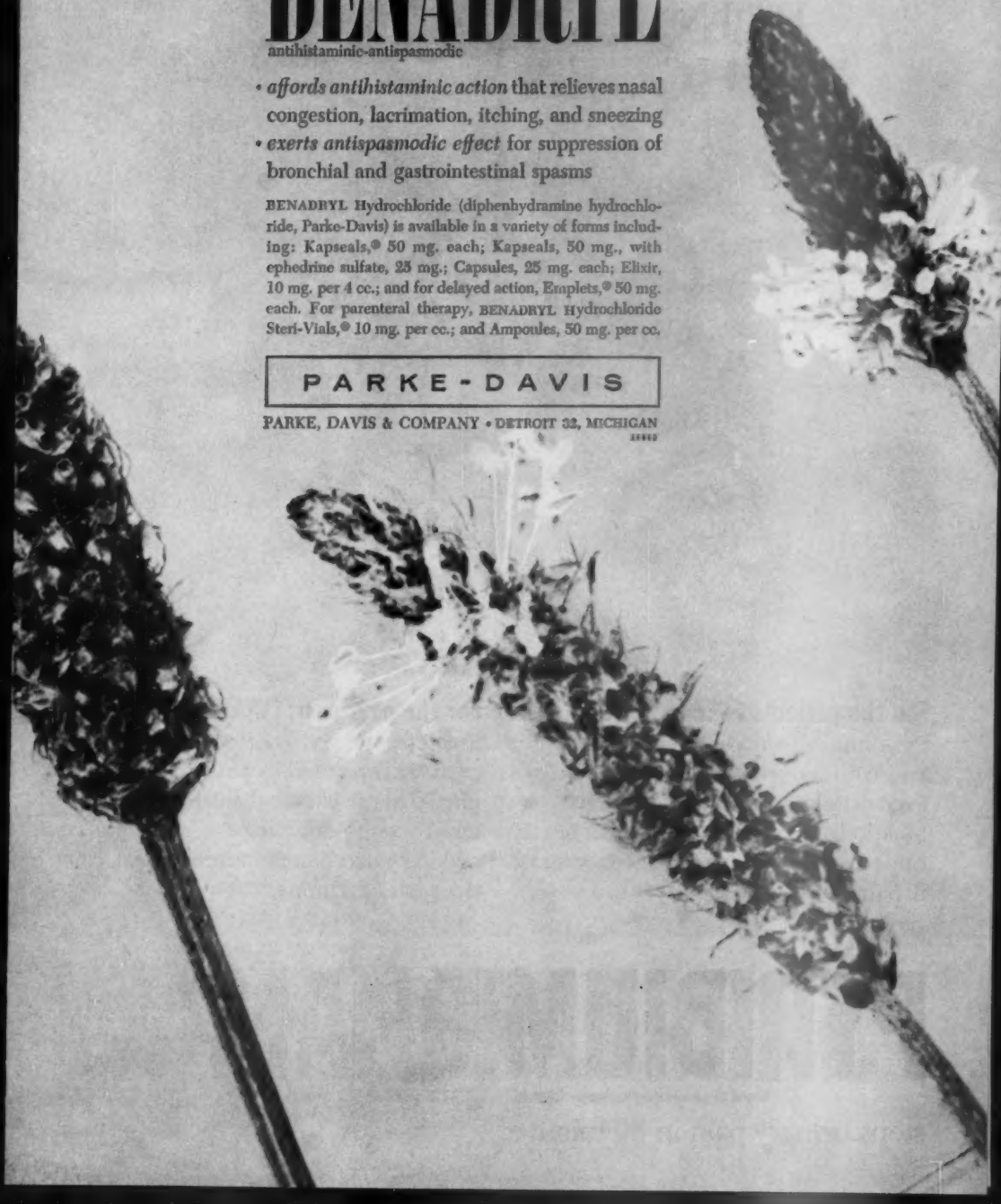

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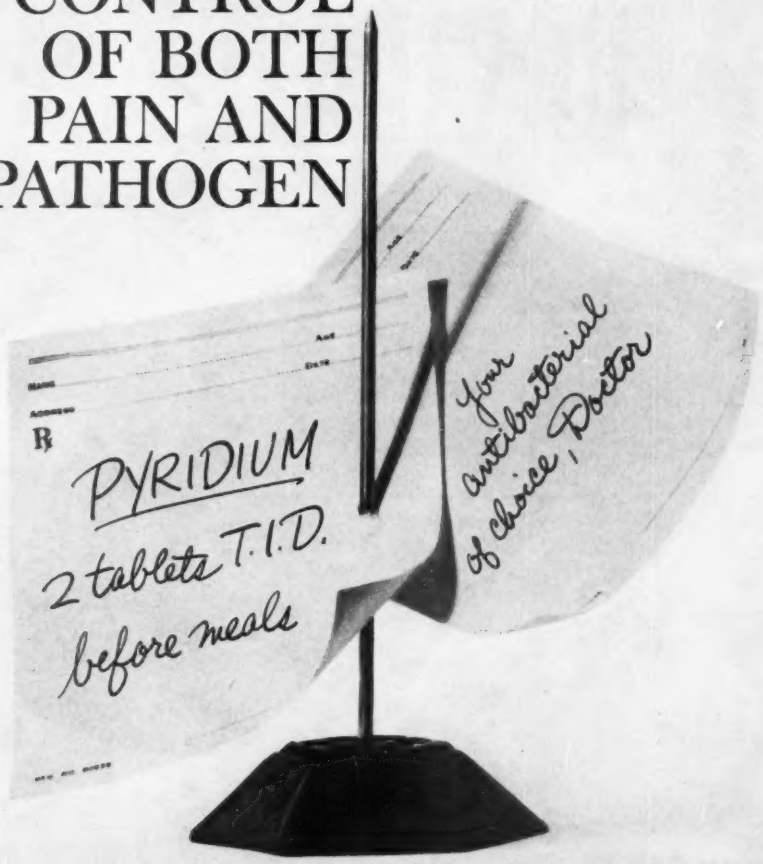
PRECISE CONTROL OF BOTH PAIN AND PATHOGEN



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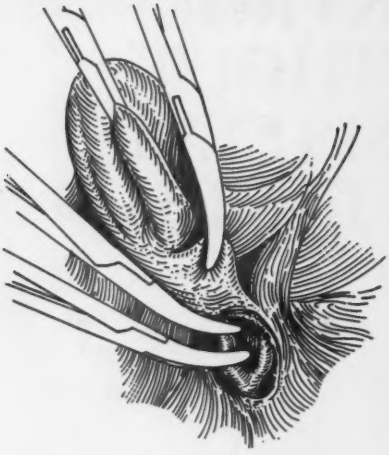

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Source: Farris, J. M., and Smith, G. K.: M. Clin. North America *43*:1133 (July) 1959.

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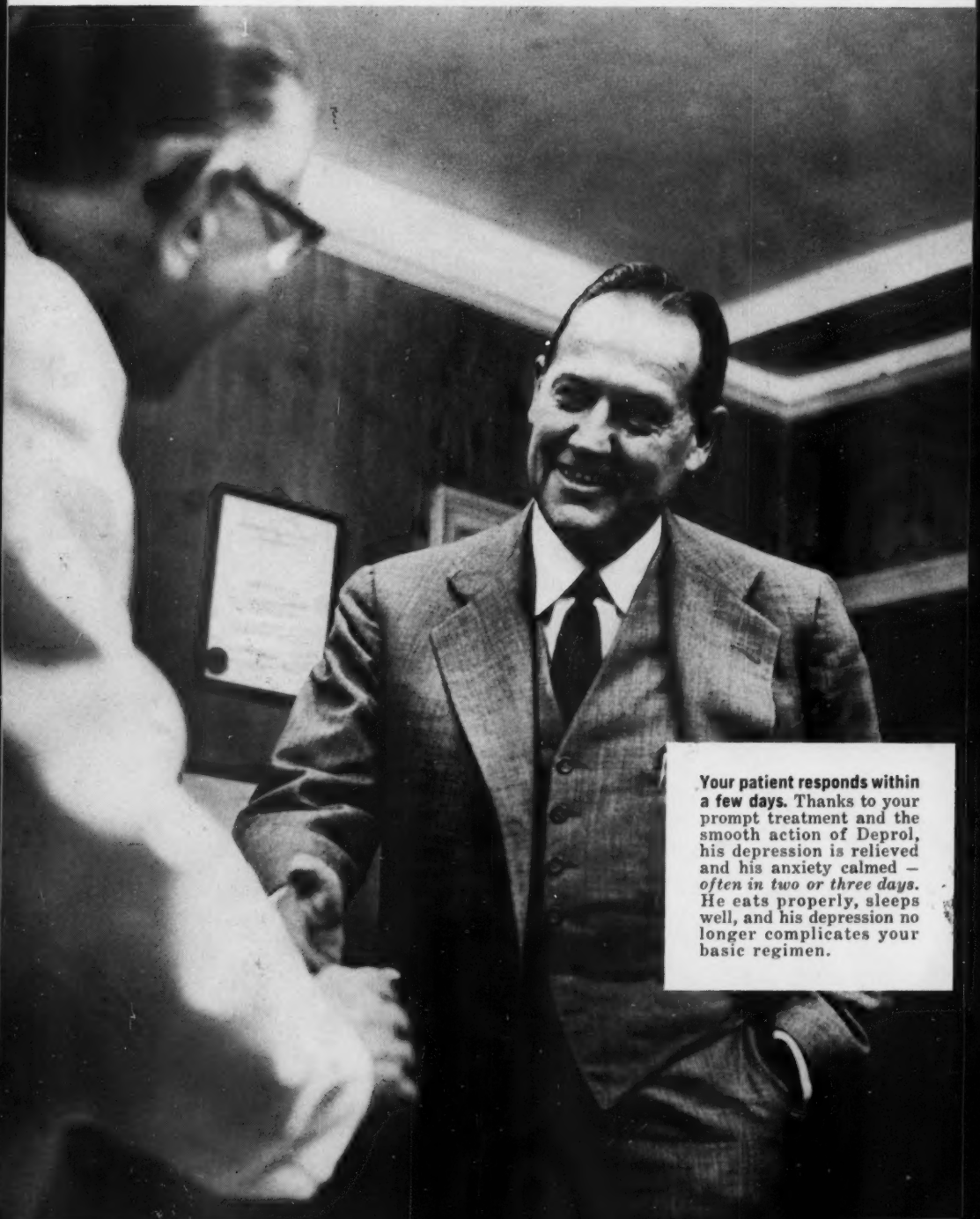

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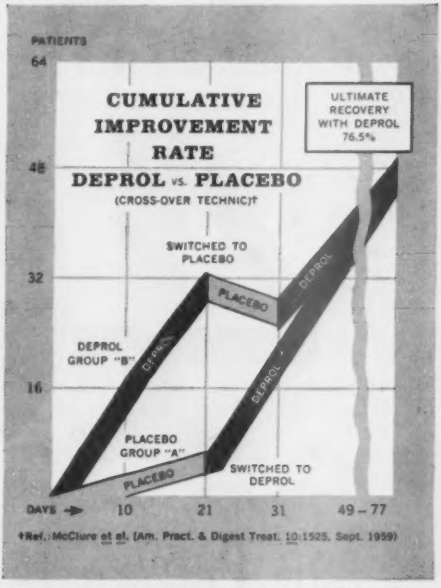
Acts safely–no danger of hypotension or liver damage. Deprol does not cause liver toxicity, hypotension, tachycardia, jitteriness, vomiting, constipation or psychotic reactions frequently reported with other antidepressant drugs. It can be safely administered with basic therapy.



Results of a controlled study of 128 patients conducted by General Practitioners, Internists, Gastroenterologists, Urologists, Surgeons, Proctologists and others in collaboration with Psychiatrists.

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Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

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Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

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BIBLIOGRAPHY *(11 clinical studies, 784 patients):*

1. Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **4.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **5.** Landman, M. E. (50 patients): Choosing the right drug for the patient. Submitted for publication, 1960. **6.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression–New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **7.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **8.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **9.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **10.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination (Deprol). Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **11.** Splittar, S. R. (84 patients): The care of the anxious and the depressed. Submitted for publication, 1959.

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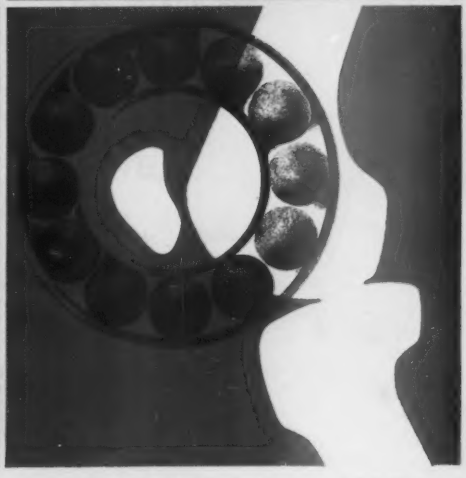

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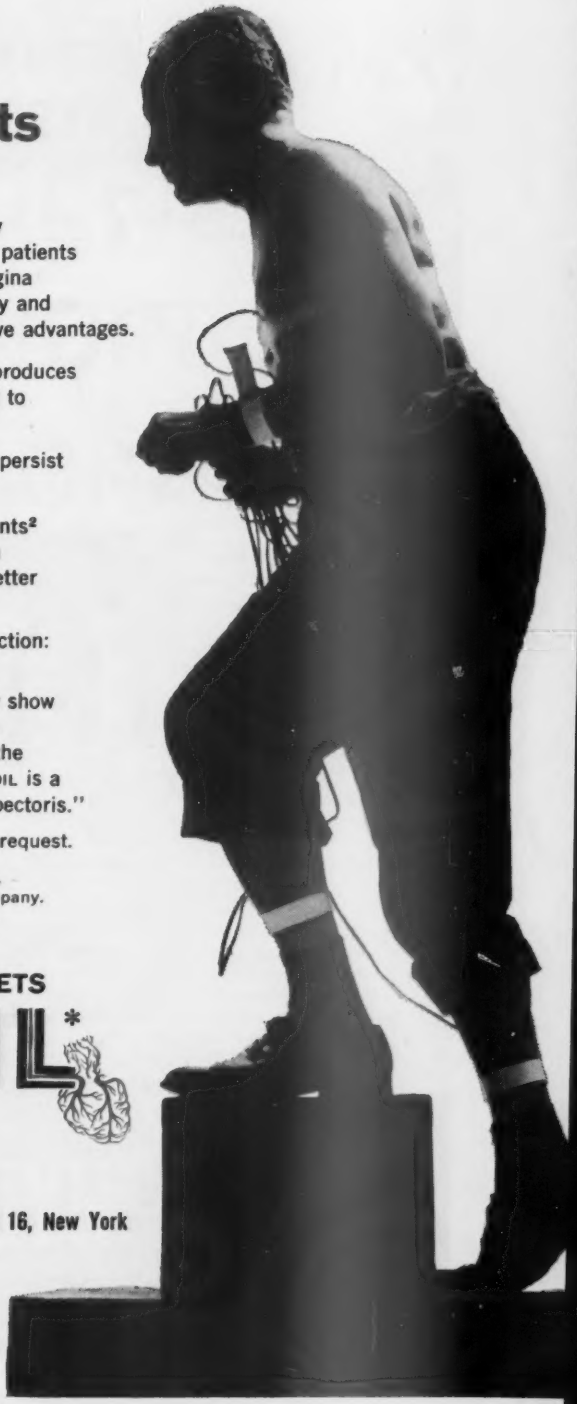

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1. Fremont, R.E.: Personal Communication (Dec., 1959).
2. Summary of Case Reports on File, Ives-Cameron Company.
3. Sherber, D.A.: Personal Communication (Oct., 1959).
4. Russek, H.I.: Personal Communication (Oct., 1959).

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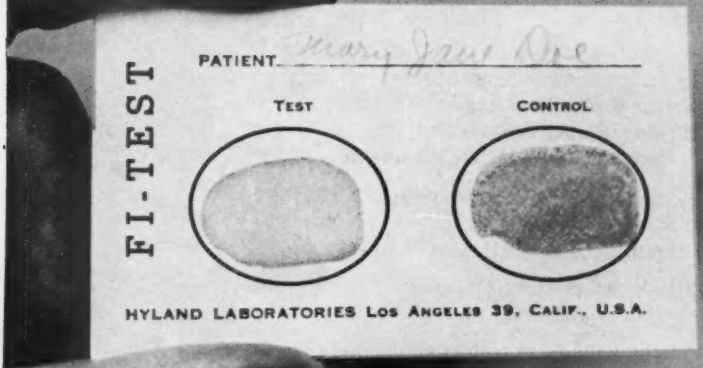

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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957. 2. Bellet, S.: Amer. Heart J. 56:479, 1958. 3. Bellet, S.: Amer. J. Cardiology 4:268, 1959. 4. Finkelstein, D.: Penn. Med. J. 61:1216, 1958. 5. DiPalma, J. R.: Progress in Cardiovascular Dis. 2:343, 1960.

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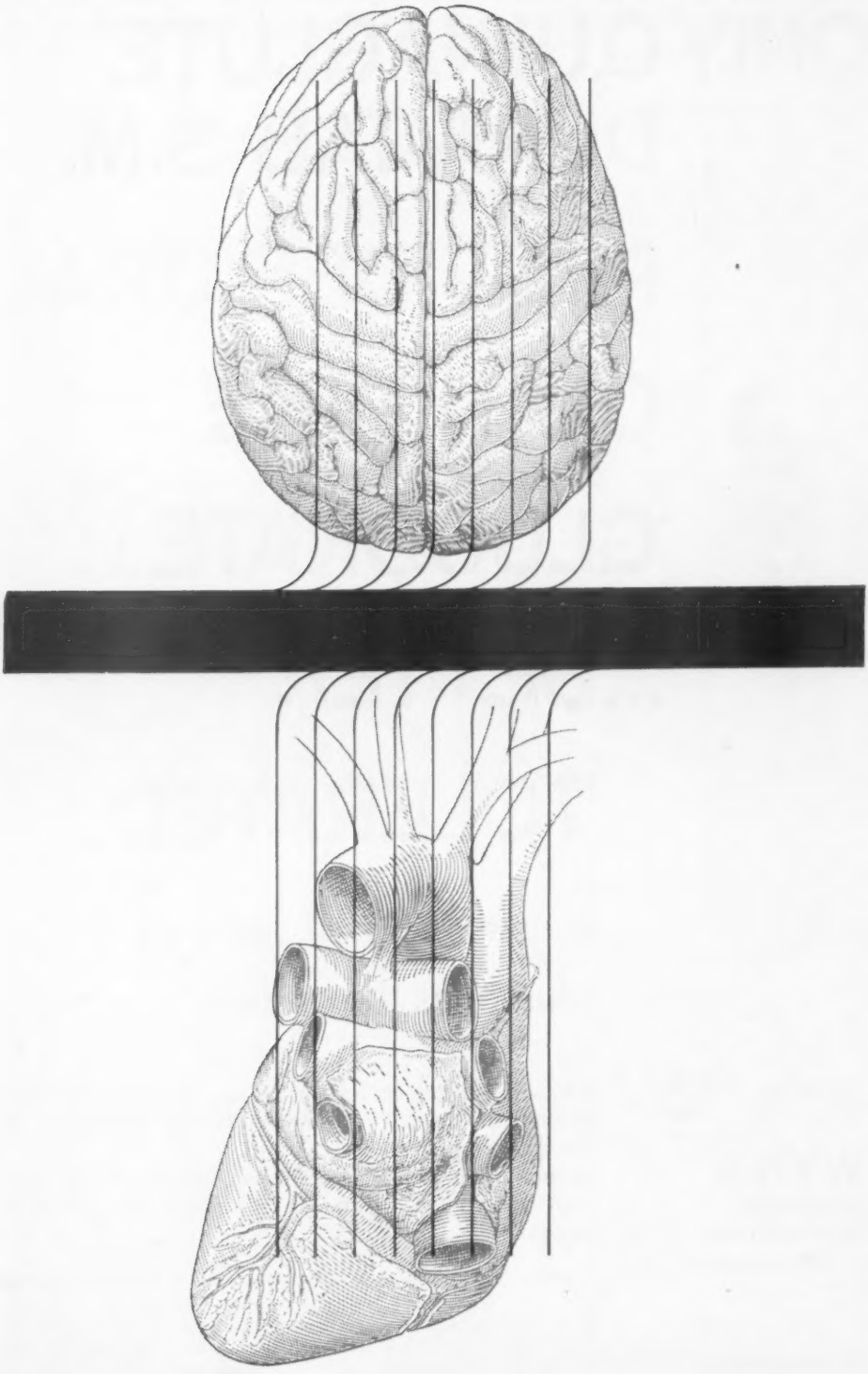

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Selected bibliography from 38 published papers: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, *Virginia M. Month.*, 87:23, 1960. 4. G. C. Griffith, *Clin. Med.*, 6:1555, 1959. 5. G. C. Griffith, *Dis. Nerv. System*, 21:(Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, *Dis. Nerv. System*, 20:(Suppl.), 26, 1959.

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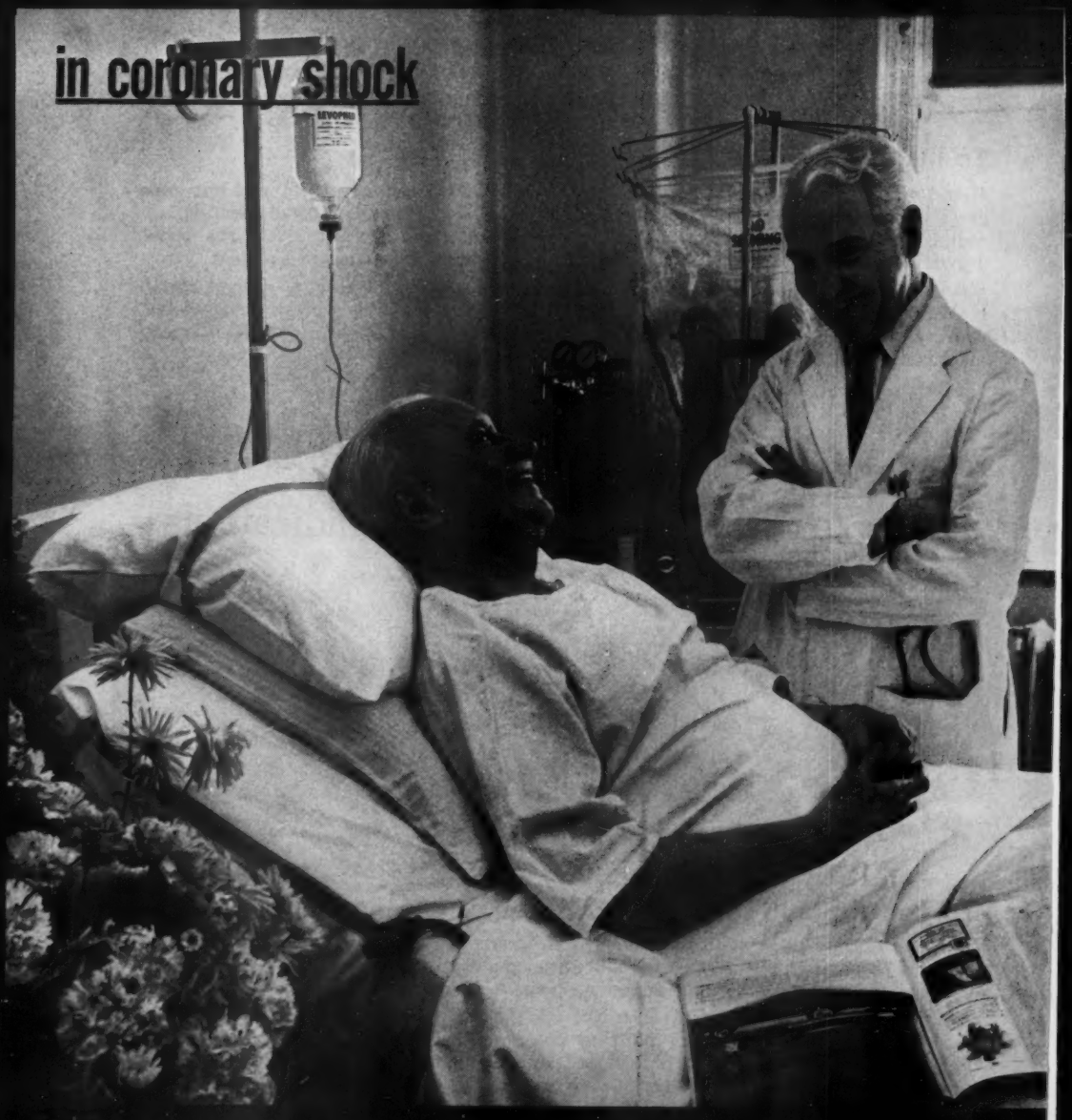

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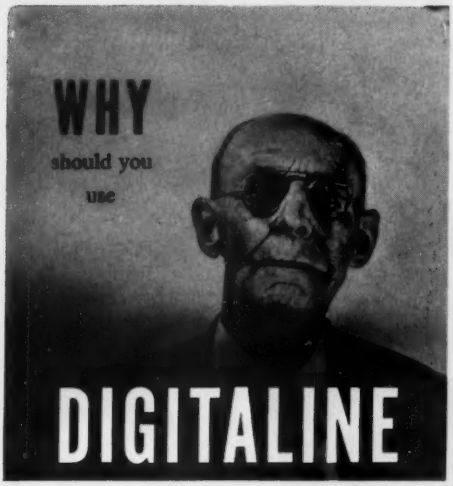

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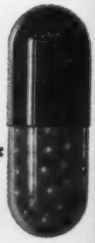

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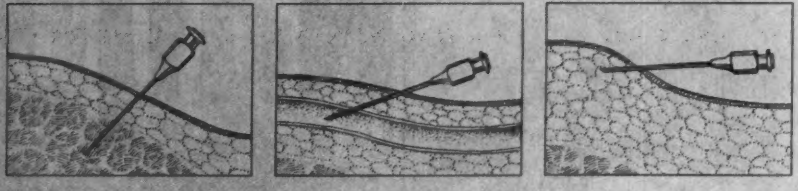

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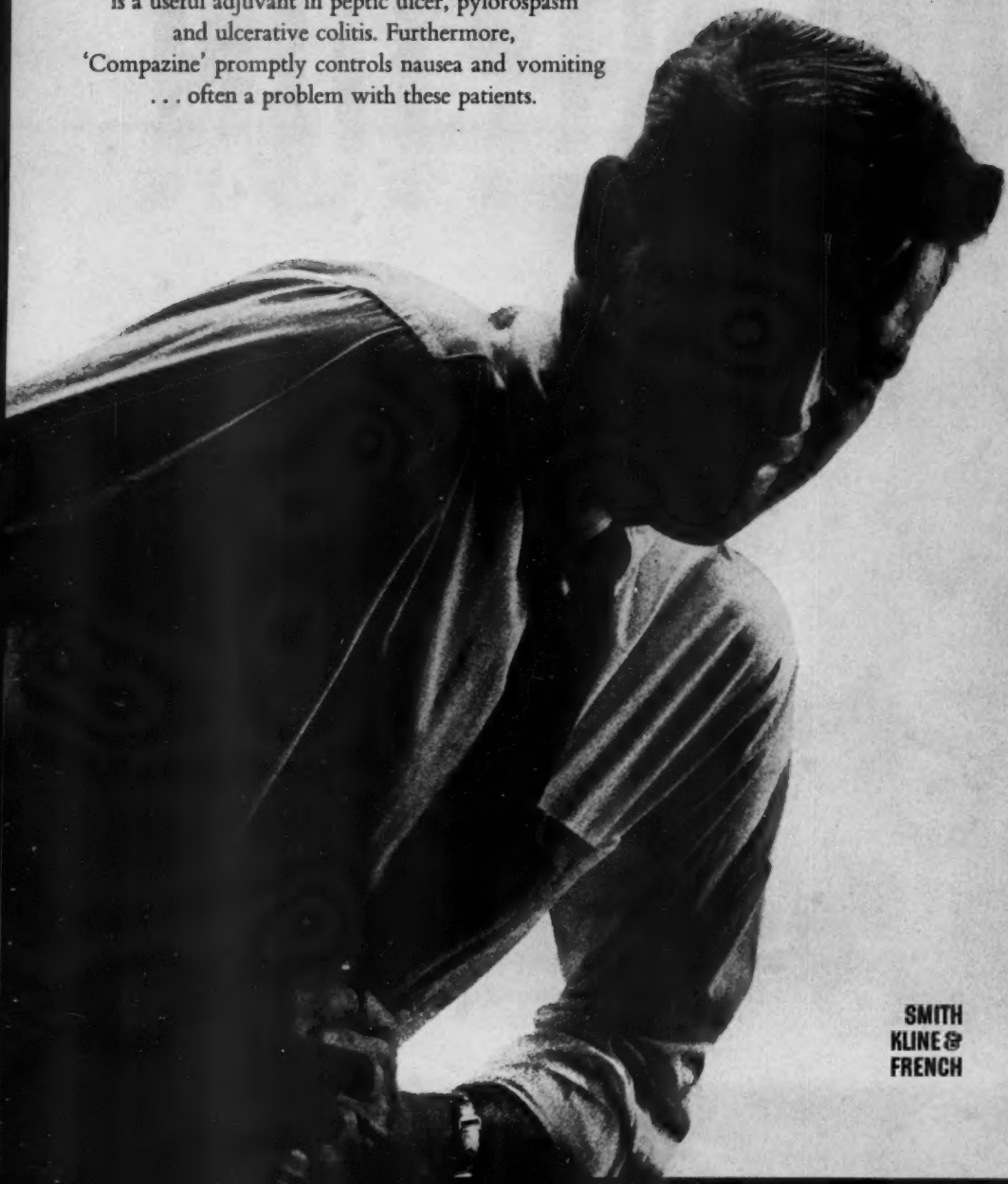

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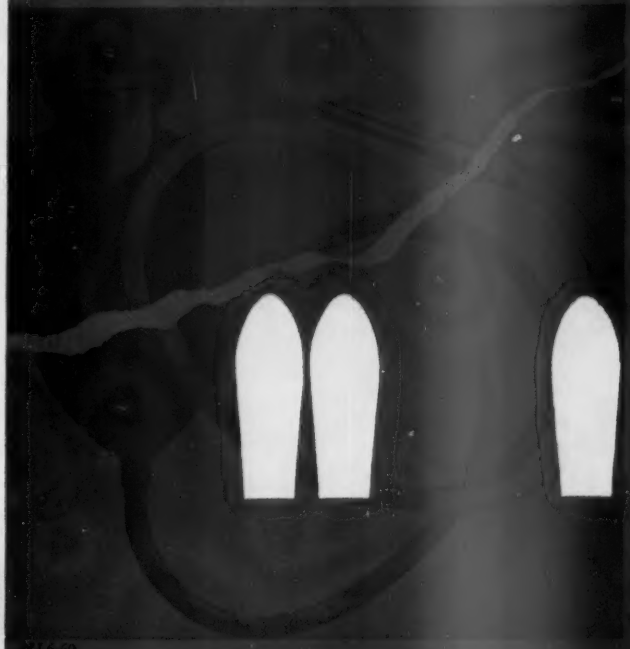

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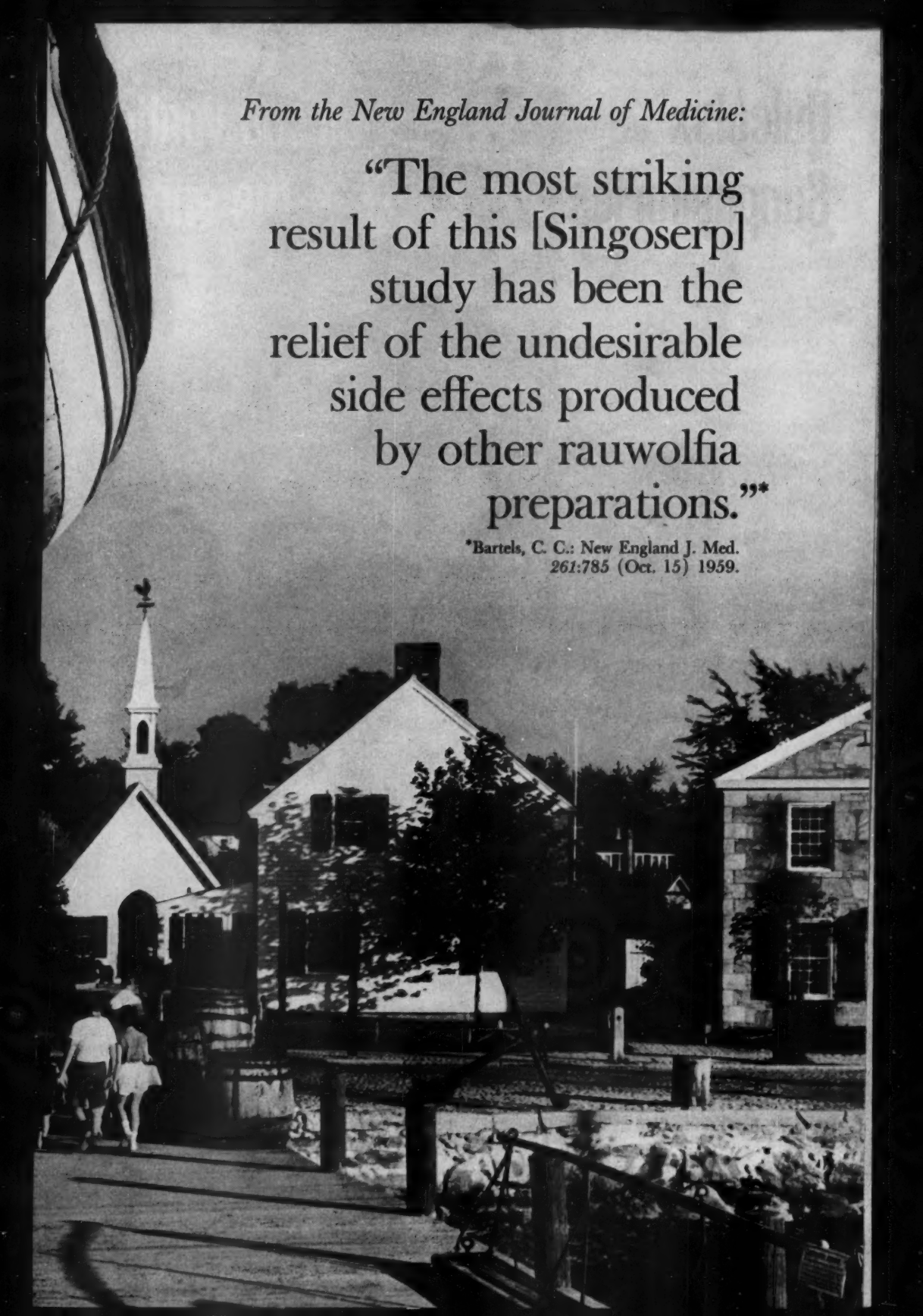

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...the first safe agent to inhibit body-produced cholesterol

...the first to lower excess cholesterol levels in both tissue and serum, irrespective of diet

DOSAGE: One 250 mg. capsule daily, before breakfast.

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THE WM. S. MERRELL COMPANY
Cincinnati, Ohio / St. Thomas, Ontario

Trademark: 'MER/29'

MER/29[1-41] is not a cholesterol-lowering agent by the usual definition. Usual measures for lowering cholesterol only modify its intake or accelerate its metabolism. Since dietary cholesterol is the minor source of total body cholesterol, results with previous agents have been limited.

MER/29, however, inhibits cholesterol biosynthesis in the liver and other tissues.[1-4] This activity is partial and takes place at a late stage in the synthesis cycle. Sufficient cholesterol remains to fulfill its role as precursor of other necessary biosynthesized substances.

Thus MER/29 is an inhibitor of excess cholesterol production, and reduced cholesterol levels in both serum[3-6] and tissues[2,4,7] is the net result of this activity. Studies of Hollander and Chobanian,[3] and those of Oaks et al.,[6] found that cholesterol levels were lowered irrespective of diet.

In clinical studies[3-6] MER/29 reduced cholesterol, on the average, 48 mg.%, and reduction ranged from 20 to 110 mg.%. Maximum reduction was reached in 5 to 8 weeks.

A report on MER/29 therapy for patients with hypercholesterolemia and its probable associated conditions:

- coronary artery disease
  (angina pectoris, postmyocardial infarction)
- generalized atherosclerosis

In some instances,[3-6] MER/29 increased exercise tolerance in patients with angina pectoris. Frequency and severity of anginal attacks were reduced, as was nitroglycerine dependence. Abnormal ECG's did not occur in these patients at the previous levels of exercise. Many of them reported improved sense of good health and well-being. Explanation of these clinical benefits is not yet known. Nevertheless, they prompt mounting interest in MER/29 as an important new agent.

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1. MacKenzie, R. D., and Blohm, T. R.: Fed. Proc. 18:417, 1959. 2. Blohm, T. R.; Kariya, T., and Laughlin, M. W.: Arch. Biochem. 85:245, 1959. 3. Hollander, W., and Chobanian, A. V.: Boston M. Quart. 10:37, 1959. 4. Kountz, W. B.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. 2:(Suppl.), 541 (May) 1960. 5. Oaks, W., and Lisan, P.: Fed. Proc. 18:428, 1959. 6. Oaks, W.; Lisan, P., and Moyer, J. H.: Arch. Int. Med. 104:527, 1959. 7. Blohm, T. R.; Kariya, T.; Laughlin, M. W., and Palopoli, F. P.: Fed. Proc. 18:369, 1959. 8-41. Additional references available on request.

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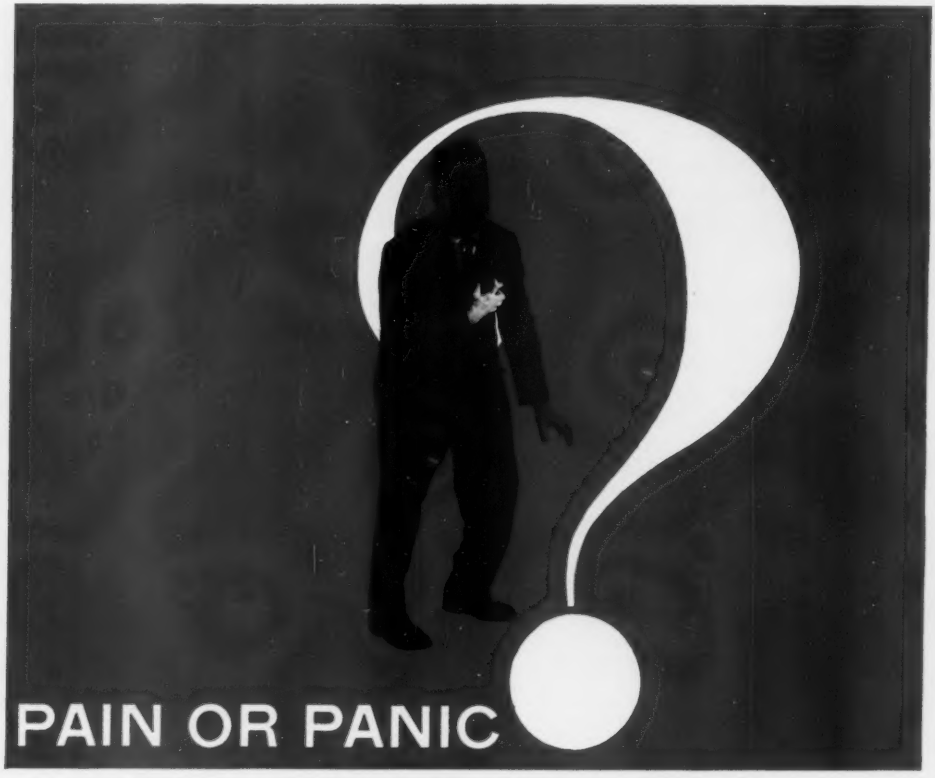

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PETN (pentaerythritol tetranitrate) is "... the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."[1]

FOR CARDIAC PANIC

"I favor ATARAX [as the tranquilizer for the anxious cardiac] ... because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."[2]

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Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX). For convenience, write "CARTRAX 10" or "CARTRAX 20." **Supplied:** In bottles of 100. Prescription only.

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

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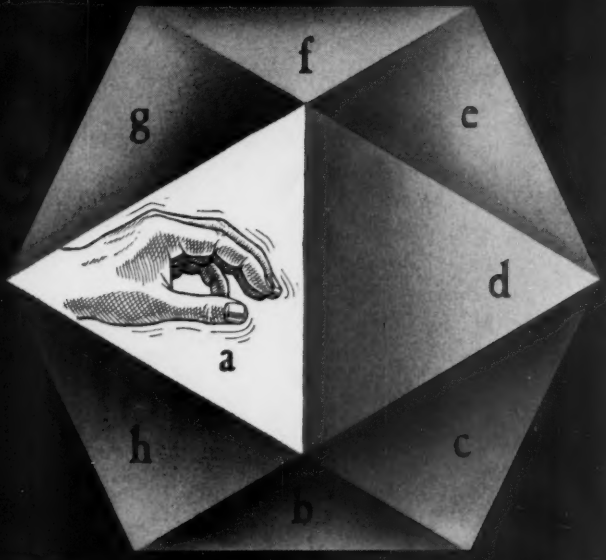

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b Energizes against fatigue, adynamia and akinesia

c An effective euphoriant

d Thoroughly compatible with other antiparkinsonism medications

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f Potent action against sialorrhea

g Counteracts diaphoresis, oculogyria and blepharospasm

h Well tolerated—even in presence of glaucoma

Dosage: usually 1 tablet (50 mg.) t.i.d. When used in combination, dosage should be correspondingly reduced.

•

Riker Northridge, California

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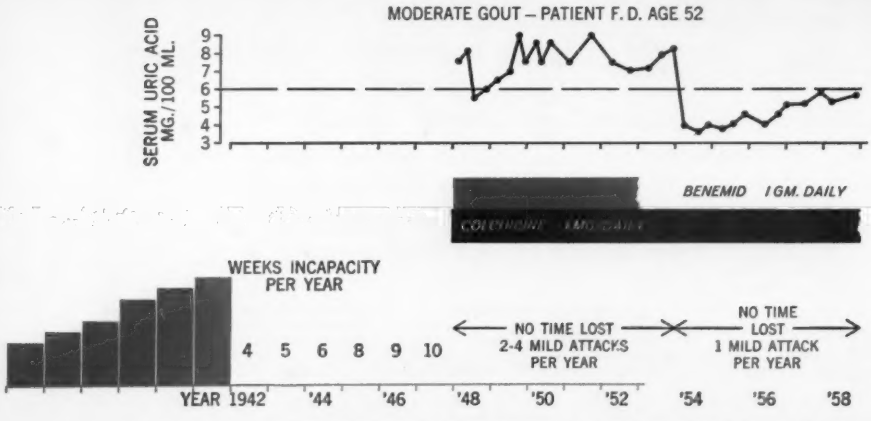
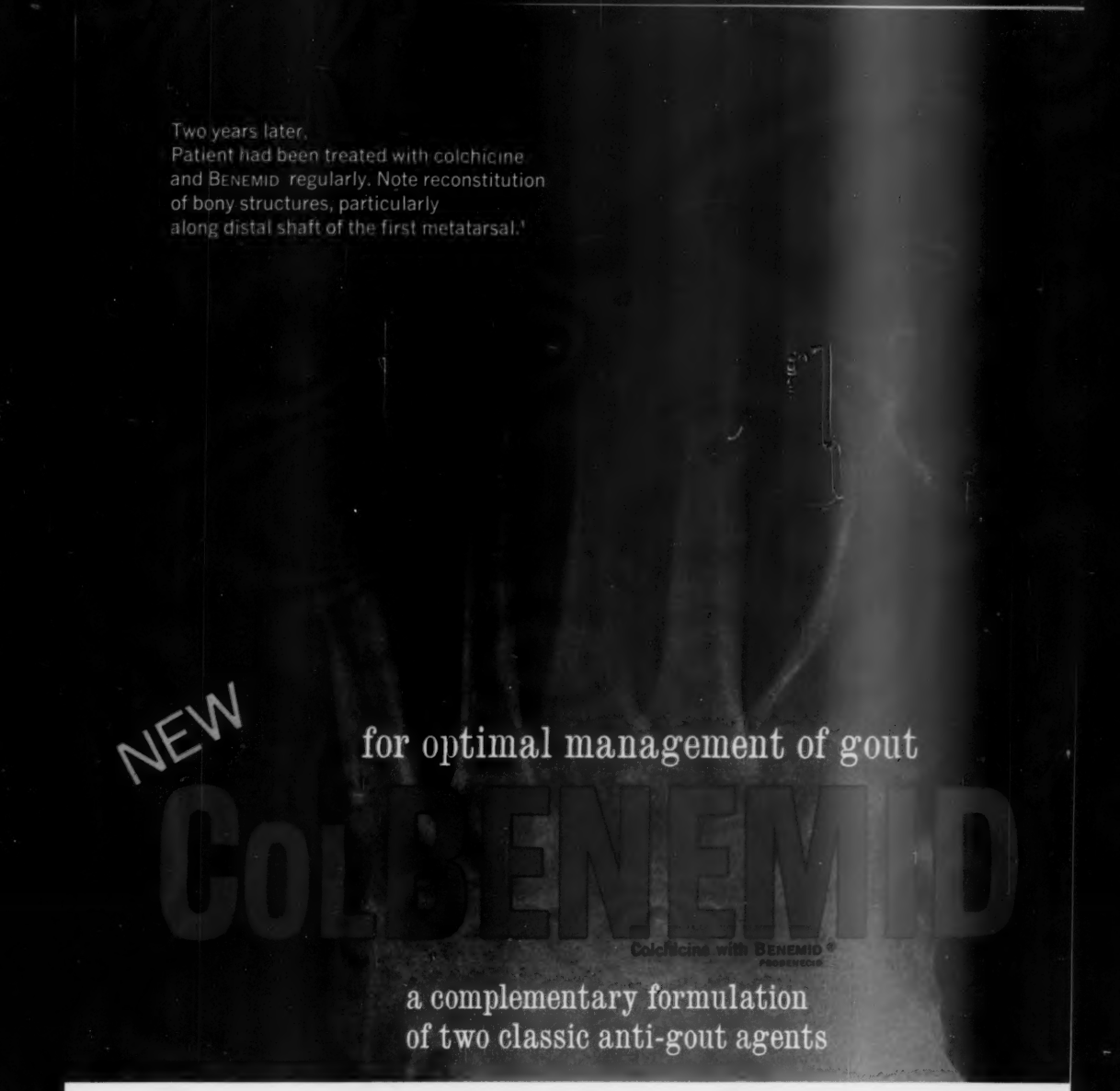
Before treatment.
Extensive gouty changes in base of proximal phalanx of great toe and in head and shaft of the first metatarsal.


MODERATE GOUT – PATIENT F. D. AGE 52
SERUM URIC ACID MG./100 ML.
9
8
7
6
5
4
3
BENEMID 1 GM. DAILY
WEEKS INCAPACITY PER YEAR
4 5 6 8 9 10
NO TIME LOST 2-4 MILD ATTACKS PER YEAR
NO TIME LOST 1 MILD ATTACK PER YEAR
YEAR 1942 '44 '46 '48 '50 '52 '54 '56 '58

Effect of colchicine and BENEMID on serum uric acid level and periods of incapacity.[2]


Two years later.
Patient had been treated with colchicine
and BENEMID regularly. Note reconstitution
of bony structures, particularly
along distal shaft of the first metatarsal.[1]

NEW

for optimal management of gout

ColBENEMID*

Colchicine with BENEMID® PROBENECID

a complementary formulation
of two classic anti-gout agents

"Prophylactic management [of gout] embodies the use of the two agents just discussed, namely, colchicine and Benemid. Each one complements the other. Neither one by itself is as effective as a combination.... Since 1950, Benemid has been available and the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[3]

Composition: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID probenecid.

Dosage between acute episodes: Mild, 1 tablet a day; moderate, 1 tablet twice daily; severe, 1 tablet three or more times daily.

Supply: Bottles of 100.

1. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, pp. 162, 163. 2. Talbott, J. H.: Gouty arthritis, Minn. Med. *42*:1044, Aug. 1959. 3. Talbott, J. H.: Recognition and treatment of gouty arthritis, Current Medical Digest *26*:57, Nov. 1959.

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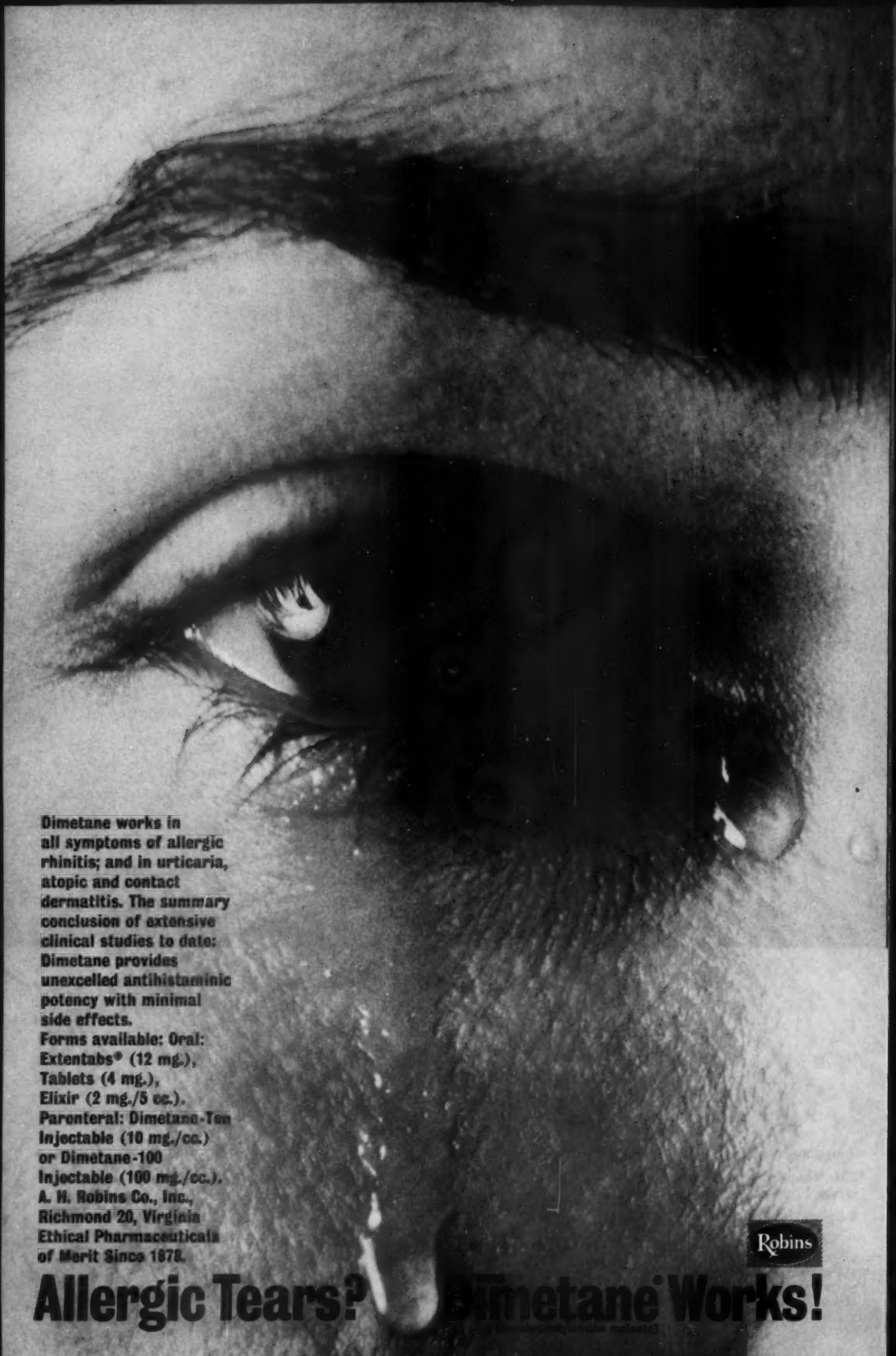
MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., WEST POINT, PA.

*COLBENEMID AND BENEMID ARE TRADEMARKS OF MERCK & CO., INC.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Forms available: Oral: Extentabs® (12 mg.), Tablets (4 mg.), Elixir (2 mg./5 cc.). Parenteral: Dimetane-Ten Injectable (10 mg./cc.) or Dimetane-100 Injectable (100 mg./cc.).
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Outstandingly Safe

For your reference: controlled studies on Miltown...

1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Halliday, A. P.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

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# of clinical use...

1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation

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3 does not produce ataxia, change in appetite or libido

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11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. **12.** Muhlfelder, W. J. *et al.*: Dis. Nerv. System 20:587, Dec. 1959. **13.** Pollak, M.: Practitioner 184:231, Feb. 1960. **14.** Rickels, K. *et al.*: J.A.M.A. 171:1649, Nov. 21, 1959. **15.** Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. **16.** Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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in today's management
of this distressing
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Outstanding characteristics of Azulfidine treatment are

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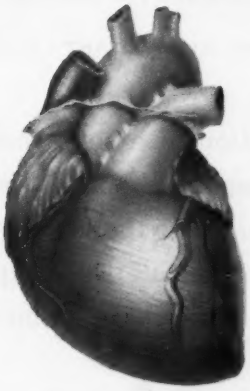
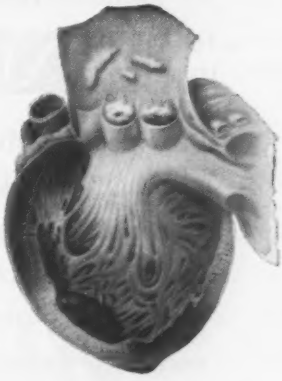


IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

...the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



AFTER MYOCARDIAL INFARCTION

...it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

Protects your coronary patient better than vasodilation alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important – Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

REFERENCES

1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J. E. F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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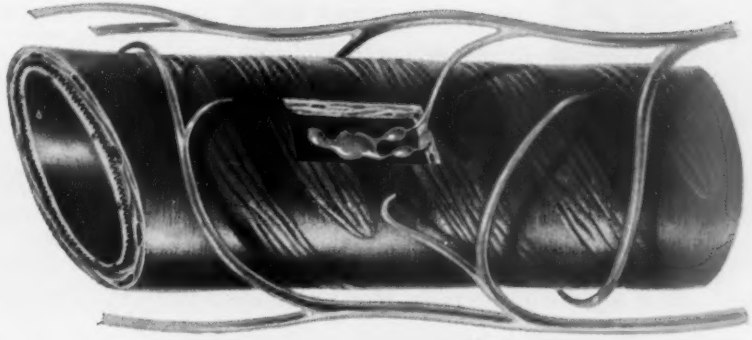
DOSAGE: For adults and children over 12, one or two capsules. For children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.

New principle: antihypertensive action at nerve-arteriole junction

ISMELIN®



*New achievement: reduces high blood pressure to near-normal levels in 80 to 90 per cent of cases**

*In 80 to 90 per cent of patients with moderate to severe (including malignant) hypertension, Ismelin—alone or combined with other antihypertensives—reduced systolic and diastolic blood pressures to normal or near-normal levels *in the standing position.*[1-3] The illustration above—a medical artist's concept of the arteriole—shows the Ismelin site of action: the nerve-arteriole junction.

For comprehensive information about this remarkable new product of CIBA research, please see the following pages.

Please Mention this Journal when writing to Advertisers

New principle, new achievement in antihypertensive therapy

Ismelin is a potent new antihypertensive agent developed by CIBA research for moderate to severe hypertension. Ismelin represents a new principle in antihypertensive therapy: It acts at the nerve-arteriole junction where it opposes the release and/or distribution of the pressor substance, norepinephrine.

This action differs markedly from that of previously available antihypertensive agents; rauwolfia compounds, for instance, inhibit norepinephrine through the central nervous system, while ganglionic blockers interrupt transmission of pressor impulses at the level of sympathetic ganglia.

Because it acts at the site of arteriolar blood pressure regulation—with no demonstrable evidence of central or parasympathetic effect—Ismelin produces a clear-cut antihypertensive response in a high percentage of cases.

Advantages **ISMELIN** *offers your hypertensive patient*

■ Almost all forms of moderate to severe hypertension can be managed with Ismelin, alone or in combination with other antihypertensives.

■ Ismelin brings blood pressure down in many persons refractory to other antihypertensive agents.

■ Ismelin lowers blood pressure in many patients who cannot be treated effectively with other potent agents because they cannot, or will not, tolerate the side effects.

■ Ismelin controls many cases of renal hypertension, often when other agents fail.

■ Patients need take Ismelin only once a day.

■ Most patients have been treated with Ismelin for prolonged periods without developing tolerance to it (although instances of tolerance have been reported).

■ Smooth absorption of Ismelin results in predictable blood pressure responses.

Please Mention this Journal when writing to Advertisers

Sites of Action: How Ismelin differs from other antihypertensive agents

Barbiturates—The cerebral cortex.

Rauwolfia compounds—The hypothalamus (with some peripheral effects).

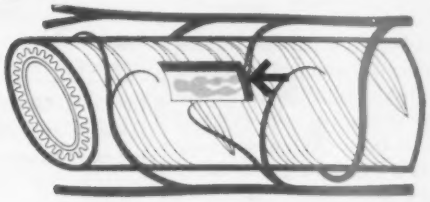
Hydralazine—The midbrain. Hydralazine prevents excessive outflow of sympathetic vasopressor impulses. In addition, it inhibits release and/or action of circulating pressor substances.

Veratrum alkaloids—The vasomotor center in the medulla, but acting only indirectly (act through a reflex from the carotid sinus).

Ganglionic blocking agents—The autonomic ganglia. Since ganglionic blockers act by blocking transmitter substance, acetylcholine, in the ganglia, these drugs also block the parasympathetic system.

Thiazide compounds—Specific site or mode of action still undetermined.

ISMELIN—Represents a new principle in the treatment of high blood pressure. Acting at the nerve-arteriole junction, Ismelin inhibits the release and/or distribution of the pressor substance, norepinephrine.



ISMELIN: *for a wide range of hypertensive patients*

Ismelin is useful in patients with moderate to severe hypertension—particularly:

- In place of other antihypertensive drugs when patients are refractory and blood pressure levels remain persistently high.
- In combination with other antihypertensive drugs when these fail to bring blood pressure down to desired levels, or to normotensive ranges.
- As a replacement for other potent agents (including ganglionic blockers) when side effects prevent effective treatment.

Please Mention this Journal when writing to Advertisers

In 80 to 90 per cent of cases[1-3]...Ismelin reduces blood pressure to near-normal levels

According to reports from more than 100 clinical investigators, Ismelin reduces blood pressure levels to normal or near-normal in a remarkably high percentage of patients. Note these typical findings:

17 of 18 patients (94.4%) treated with Ismelin become normotensive in the erect position.

Page and Dustan[1] gave Ismelin orally, alone or in combination with other antihypertensive drugs, to 18 patients daily for 2 to 12 weeks.

RESULTS: All 18 patients had reductions in standing blood pressure; 16 had reductions in supine blood pressure as well. In 17 of the 18 cases, blood pressure levels became normal or near-normal in the erect position.

Average Standing B.P.
Control pressures ..... 173/115 mm. Hg
Results with Ismelin ..... 131/85 mm. Hg
(during last week of treatment)

In 14 of 15 patients (93.3%) on Ismelin, blood pressure reduced to normal or near-normal levels in the standing position.

Ismelin was administered orally by Frohlich and Freis[2] for 4 to 9 weeks to 15 male patients selected from the hypertensive clinic. All previous antihypertensives were discontinued for a period of 2 weeks.

RESULTS: Ismelin evoked a potent antihypertensive response in the erect position: the blood pressure of 14 of the 15 patients dropped to normotensive or near-normotensive levels. "The response [to Ismelin] was characterized by a potent, orthostatic, antihypertensive effect similar to that seen with the ganglionic blocking drugs but without the side-effects of parasympathetic blockade."[2]

Average Standing B.P.
Pretreatment pressures ..... 181/122 mm. Hg
Results with Ismelin ..... 132/90 mm. Hg

In 15 of 18 subjects (83.3%), Ismelin reduced high blood pressure to near-normotensive levels.

Ismelin was administered orally by Richardson and Wyso[3] to 18 male hospitalized patients with hypertension. Complications included hemorrhages, exudates or papilledema of the optic fundi. Ten had BUN above 25 mg. per cent "...and six had previously failed to respond to ganglionic blocking drugs and chlorothiazide in the hospital."[3]

RESULTS: "All patients showed definite reduction in blood pressure coincident with administration of Ismelin. In most of the subjects [15], standing blood pressure could be maintained near normal levels."[3]

Average Standing B.P.
Control pressures ..... 195/129 mm. Hg
Results with Ismelin ..... 139/89 mm. Hg

"Side-effects encountered... have indeed been minimal..."[4]

Brest and Moyer[4] state: "Side-effects [of Ismelin] encountered to date have indeed been minimal, with mild diarrhea as the only significant complaint even when large daily doses (450 mg.) of the drug are administered. No evidence of toxic action of the drug has been encountered thus far." Page[5] observes: "...Guanethidine [Ismelin] has the advantage [over ganglionic blockers] in that it is much easier to handle and does not produce nearly as much dose sensitivity. Too much of a ganglion-blocking agent will really 'clobber' the patient; with Guanethidine, there is much more leeway." Kirkendall and co-workers[6] report: "Guanethidine has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy." Leishman and associates[7] conclude: "The capacity of guanethidine to reduce the blood-pressure of hypertensive patients without symptoms of parasympathetic blockade is consistent with a mechanism of selective sympathetic-nerve inhibition..."

How to use Ismelin:

Precautions: Ismelin is a potent drug, and its misuse can lead to disturbing and serious clinical problems. Physicians should familiarize themselves with the details of its use before prescribing. Ismelin is contraindicated in patients with a pheochromocytoma for two reasons. Since Ismelin initially causes the release of norepinephrine, it may cause a release of the hormone from the tumor, causing a precipitous blood pressure rise. The effect of norepinephrine is augmented by prior treatment with Ismelin, so the release of the hormone by the tumor in a treated patient would have an adverse effect.

Dosage: *Ambulatory Patients*—Individualization of dosage is essential for optimal results. Blood pressure should be taken in both the supine *and the standing position* at every visit and increases in dosage made only if there has been *no* decrease in standing blood pressure from the previous levels. Average daily dose is 25 to 50 mg. A single daily dose is generally most convenient.

Dosage Chart
for Initiating Ismelin in Ambulatory Patients

VISITS AT INTERVALS OF 5 TO 7 DAYS	DAILY DOSE
Visit No. 1 (Start with 10-mg. tablets)	10 mg.
Visit No. 2	20 mg.
Visit No. 3 (Patient can be changed to 25-mg. tablets whenever convenient)	30 mg. (three 10-mg. tablets.) or 37½ mg. (one and one-half 25-mg. tablets.)
Visit No. 4	50 mg.
At Visit No. 5, and subsequent visits, the dosage may be increased by 12.5 mg. or 25 mg. if necessary.	

The dosage should be reduced in any one of the following three situations:

1. *Normal supine pressure.* Since Ismelin may have a cumulative effect, it is both desirable and necessary to use the lowest effective dosage.
2. *Excessive orthostatic reduction.*
3. *Severe diarrhea.* While some increase in bowel movements can be easily controlled, severe diarrhea is a sign of overdosage.

Side effects: Patients may develop postural hypotension. While symptoms can be minimized by careful dosage adjustment, some patients will experience lightheadedness and dizziness. In patients with severe symptoms, Ismelin should be withheld and should be resumed at lower doses when all symptoms have cleared.

Unlike ganglionic blockers, Ismelin does not cause *impotentia erigendi.* Ejaculation, however, is sometimes completely inhibited.

Diarrhea has been bothersome in some instances; it is frequently controlled with lower doses or with Antrenyl, 5 mg. t.i.d. Other side effects reported in a few patients: mild edema, nasal congestion, fatigue and weakness.

For more complete information on precautions, dosage, and side effects, write to Medical Service Division, CIBA, Summit, N. J.

Supplied: *Tablets,* 10 mg. (yellow, scored) and 25 mg. (white, scored).

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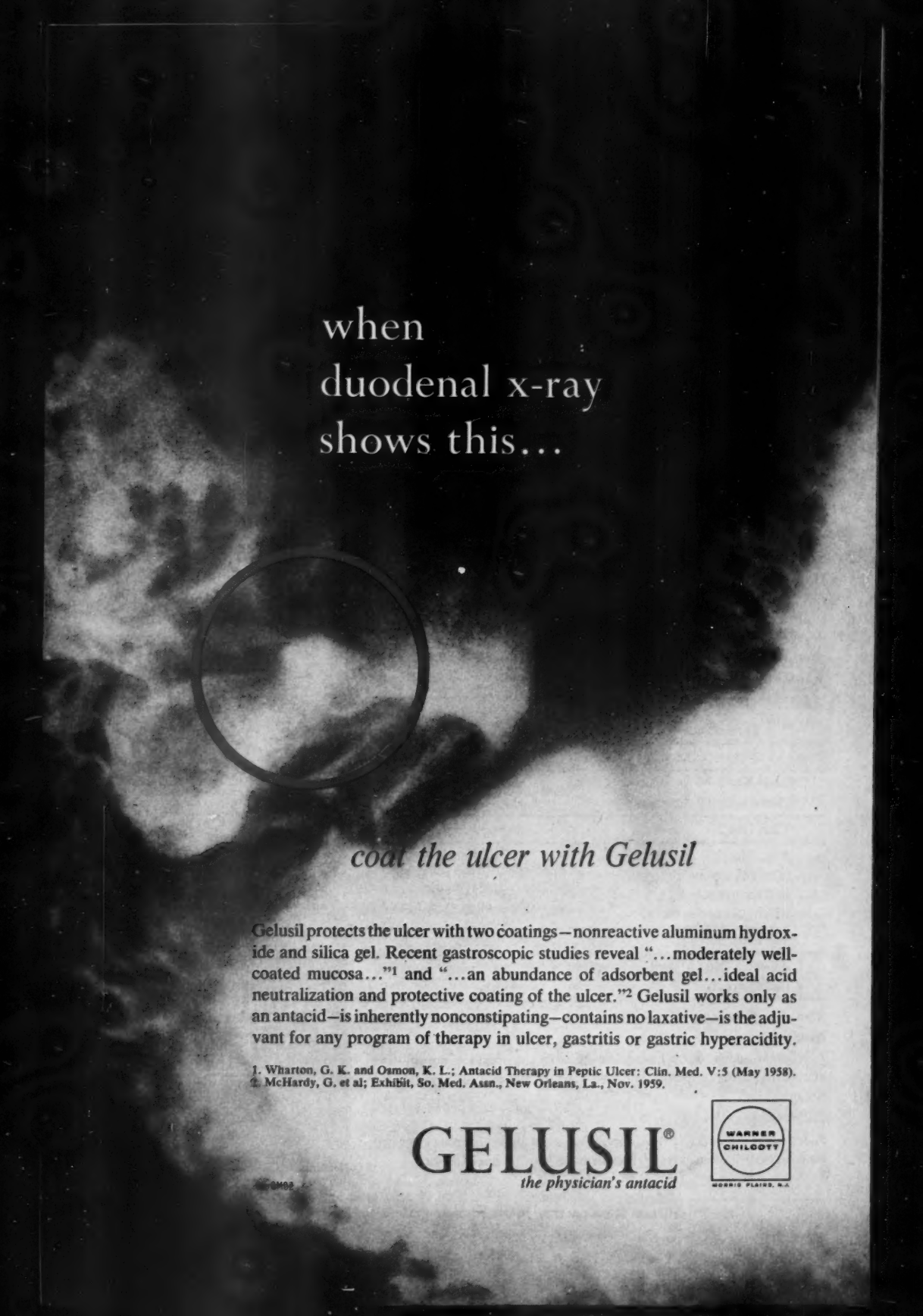
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1. Wharton, G. K. and Osmon, K. L.; Antacid Therapy in Peptic Ulcer: Clin. Med. V:5 (May 1958).
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ANNALS OF INTERNAL MEDICINE

VOLUME 53 AUGUST, 1960 NUMBER 2

SOME CLINICAL ASPECTS OF LIFE AT HIGH ALTITUDES *

By ALBERTO HURTADO, M.D., *Lima, Peru*

CONTINUOUS exposure to a high-altitude environment, where the lowered partial pressure of the oxygen in the inspired air originates a certain degree of hypoxia, demands some adaptative mechanisms. These, in general, and in their main objectives, introduce an economy in the drop of the pO_2 gradient from alveolar air to tissue level, and make possible the acquisition and utilization of the oxygen in the cell metabolism. In our experience, and from observations carried out mainly in Morococha, Peru, at an altitude of 4,540 meters (14,900 feet), with an average barometric pressure of 444 mm. Hg, these mechanisms attain their highest degree of efficiency in the Indian natives, born and living permanently at a high level.[1] There is some evidence [2] that chemical processes in the tissues have a fundamental importance in what may be called "natural acclimatization."

But a high-altitude environment is not only a fertile field to study tolerance to hypoxia. When this is permanent, it may also give rise to functional and organic alterations, and may influence the development and characteristics of certain conditions which may be considered to be of a pathologic or clinical nature. We will comment very briefly on some of these latter aspects.

It has been demonstrated [3] that healthy people living permanently at high altitudes have a moderate but constant degree of pulmonary hypertension, in contrast to the presence of low systolic and diastolic pressures in the peripheral circulation (figure 1). The factors responsible for this elevation

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of pulmonary blood pressure are not as yet well defined. The administration of oxygen during the time of cardiac catheterization does not modify the mean pulmonary artery pressure. The cardiac output has rather low

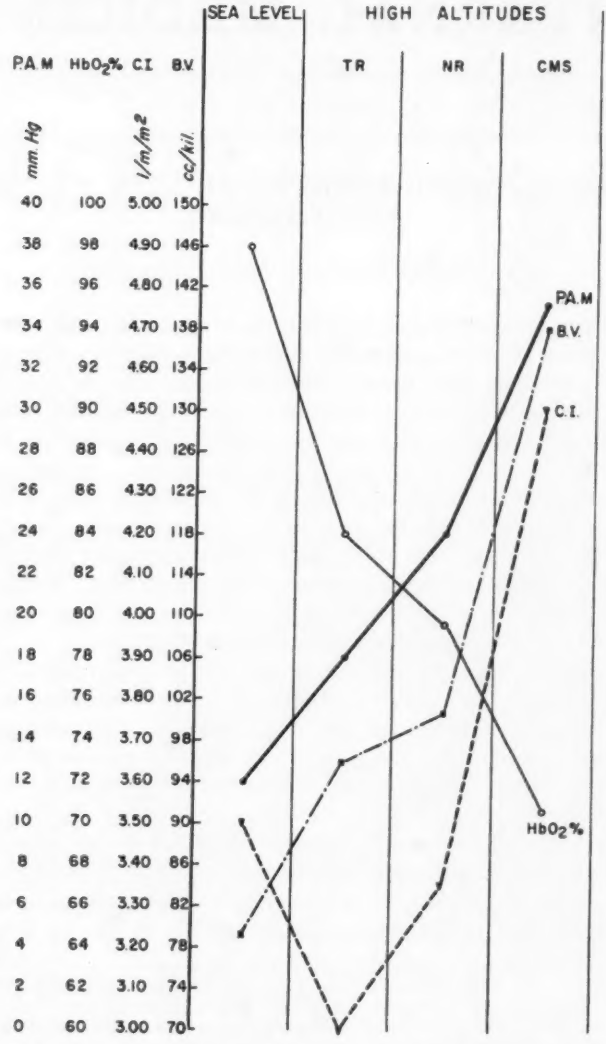

FIG. 1. Relationship between mean values of arterial oxygen saturation ($HbO_2\%$), cardiac index (L./min./m²), blood volume (c.c./Kg.) and mean pulmonary artery pressure (mm. Hg) at sea level and in different groups of subjects studied at an altitude of 14,900 feet. TR: temporary residents (one year); NR: native residents; CMS: chronic mountain sickness. (Reprinted by permission from the J. Appl. Physiol. **9**: 328, 1956.)

normal values in the healthy residents at high altitudes and, in consequence, is not a contributing factor. An increase in the volume of the blood contained in the lungs, an observation made in Morococha residents,[4] and lack of a corresponding distensibility in the vascular bed of these organs, may have an etiologic role. It must be pointed out, however, that the reserve capacity to accommodate an increased blood volume in the lesser circulation is still a controversial issue.

Closely related to the special hemodynamic characteristics of the pulmonary circuit are some interesting features in the electrocardiographic tracings of people living at high altitudes. These have been extensively investigated,[5] and have been interpreted as representing right ventricular hypertrophy, an assumption verified by anatomic studies.[6] Recently, Peñaloza and others [7] have extended this type of investigation to a study of the very young and, using electrocardiographic and vectorcardiographic procedures, have demonstrated that the electrical activity of the heart in infancy and childhood is not similar at high altitudes and at sea level. The difference becomes evident some weeks after birth, and is permanent. These investigators assume that pulmonary hypertension is also present at that age period and is probably associated with persistence of the fetal structure of the pulmonary arteries and arterioles.

The native resident in high altitudes may lose his high degree of tolerance to the low-pressure environment and exhibit a series of alterations and symptoms which have been grouped under the general classification of "chronic mountain sickness." The loss of natural acclimatization is not a frequent occurrence but, on the other hand, neither is it a rare finding in the population of the high Andean region of Peru. There is no age limit, and cases have been described in childhood and in old age, but in our experience there is a greater incidence in relatively young adults. The syndrome was originally described by Monge [8] in 1928, and its physiopathologic characteristics have been subsequently pointed out.[9, 10]

The signs and symptoms which indicate a loss of acclimatization may be of a quite varied nature, and apparently it is not possible to group all cases into a single clinical entity. However, most cases show very striking and constant features. There is a considerable increase in the circulating blood volume, due entirely to an elevated cell component (figure 2). The plasma volume is markedly decreased. Bone marrow biopsies show a hemopoietic hyperactivity which affects the erythropoiesis exclusively. The leukocyte and platelet development and concentration in the peripheral blood are normal, in contrast with the marked rise in the red cell count, hematocrit and hemoglobin. Values of 80% hematocrit for the red blood cells, and of about 24 to 26 gm. of hemoglobin per 100 c.c. of blood, are not infrequent, and are associated with a very high viscosity. The greater production of erythrocytes is balanced by a proportionally increased rate of cell destruction, as shown by an elevated pigment excretion in urine and feces.[12]

Circulatory observations in cases of chronic mountain sickness have revealed a very marked evidence of right heart hypertrophy in the electrocardiographic tracings. The cardiac output, in contrast with that of the healthy native residents, is elevated, and the degree of pulmonary hypertension is also more accentuated (figure 1). The systolic and diastolic pressures in the peripheral circulation are very low. The investigation of

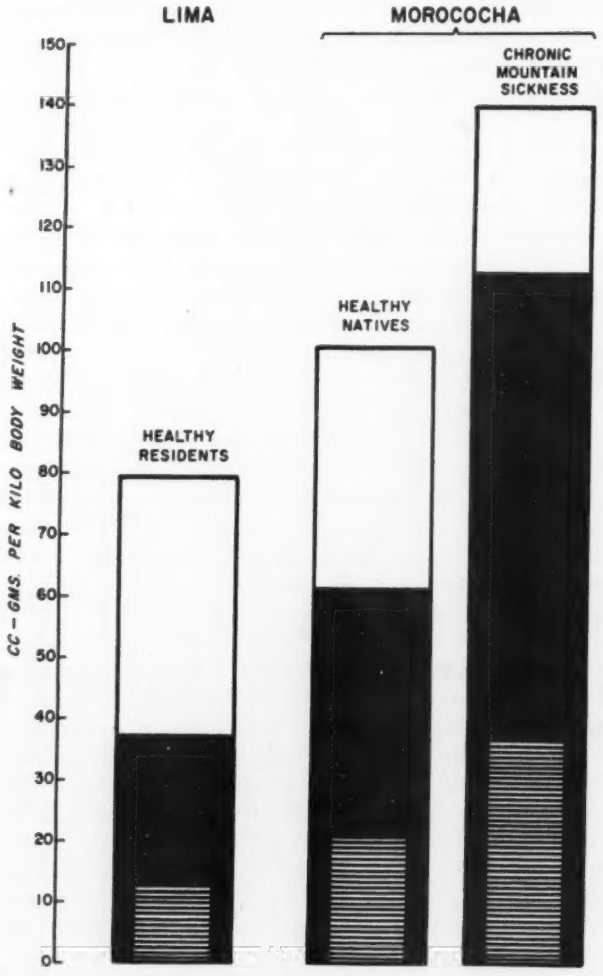

FIG. 2. Total mean blood volumes (determined with Evan's blue): mean values in Lima (20 subjects), at sea level, and in Morococha, at 14,900 feet of altitude: in healthy native residents (20 subjects) and in patients with chronic mountain sickness (four cases). White area: plasma volume; black area: cell volume; crossed area: hemoglobin.

the respiratory function in these cases has produced important data. The degree of arterial oxygen saturation is below the level which corresponds to the altitude where the patient lives. The increased hypoxia may be very severe, and values between 60 and 70% for arterial HbO_2 have been observed. For a long time it was believed that this abnormal accentuation of the blood oxygen unsaturation was due to an impaired gas diffusion through a thickened alveolar membrane. However, this assumption has not been wholly verified in recent determinations of the A-a gradient at different levels of oxygenation. This gradient seems to be only moderately increased.

The total pulmonary capacity is not significantly changed, with the exception of a moderate reduction in the vital capacity. The residual air volume falls within the normal limits established for high-altitude residents. The most significant respiratory alteration found in chronic mountain sickness is absence in most cases of the hyperventilation observed in all healthy subjects exposed to a low-pressure environment (figure 3). This process elevates the alveolar pO_2, thus compensating in some degree for the decrease brought about by the low barometric pressure. The relative hypoventilation, associated with the loss of acclimatization, present at rest and during physical activity, is responsible for the low alveolar pO_2 found in chronic mountain sickness; this, in turn, originates an accentuation of the arterial blood unsaturation, because the oxygen exchange in the lungs, at that level of altitude, operates on the descending part of the dissociation curve, where a small variation in pO_2 is met with a high reduction in the uptake of such gas by the blood. The acid-base balance of the arterial blood in these cases is characterized by a moderate lowering of the pHs, the result of an elevated pCO_2 and a normal concentration of bicarbonate. It corresponds to a condition of respiratory acidosis uncompensated.

The finding of hypoventilation in most cases of chronic mountain sickness directed our study to the response of the respiratory center to chemical stimulation. A considerable number of observations [1] has demonstrated that, at high altitudes, the center shows a greater ventilatory response to the administration of CO_2, and that this is more pronounced in temporary residents than in natives; but in both cases the difference from that in men living in a normal pressure environment is very evident. The data accumulated have shown that in chronic mountain sickness there is a decrease in the ventilatory response to the breathing of CO_2 or, in other words, a decreased sensitivity of the respiratory center to such chemical stimulation (figure 4). There is some individual variability in the degree of the decreased response. In some cases this is very marked. Oxygen administration simultaneous with the CO_2 inhalation does not alter the decreased sensitivity (figure 5), and in these circumstances we have even observed an accentuation of the hypoventilation. It may also be pointed out that the

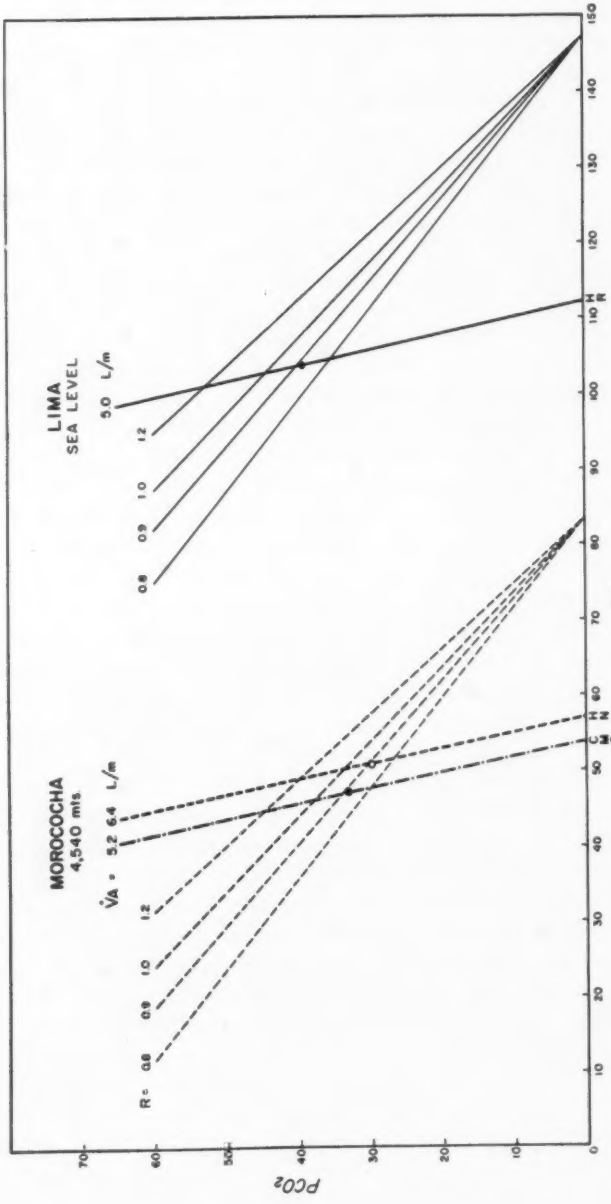

FIG. 3. Oxygen-carbon dioxide diagram of Rahn-Fenn. Position of the mean alveolar gas pressures, and the corresponding values in R.Q. and in VA (relative alveolar ventilation in L./min.) in healthy residents in Lima at sea level (NR); in healthy natives (HN) of Morococha at an altitude of 14,900 feet; and in cases of chronic mountain sickness (CMS), also studied in Morococha. The R.Q. and the isoventilation lines have been constructed from the alveolar air and the alveolar ventilation equations.

duration of the voluntary apnea tends to be markedly prolonged in these patients.[10]

The pathogenesis of the hypoventilation in chronic mountain sickness remains unexplained. It is interesting to mention in this connection the frequent description in the medical literature of recent years of cases of obesity at sea level who show hypoventilation, hypoxia and polycythemia.

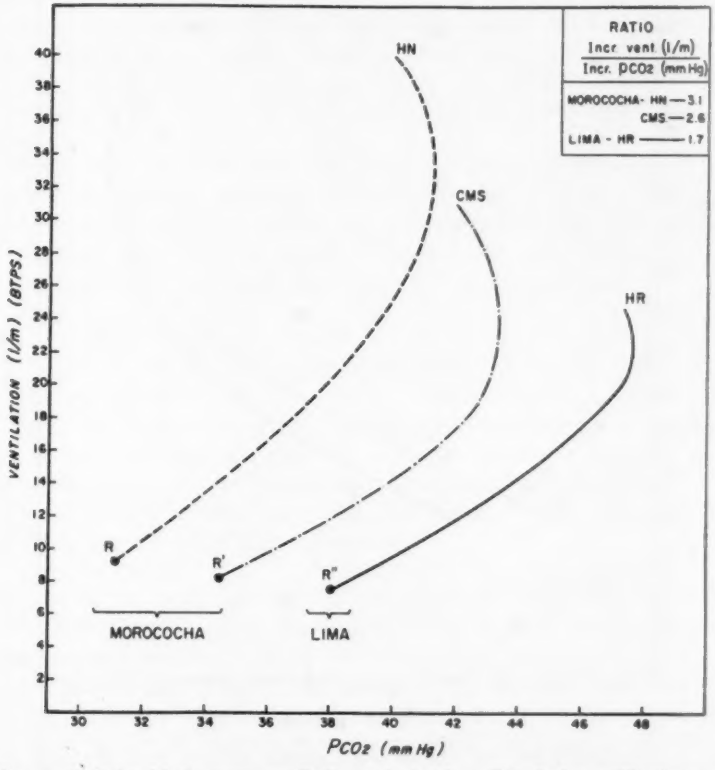

FIG. 4. Relationship between ventilation and alveolar pCO_2 during a 15-minute period of CO_2 breathing. The curves correspond to the mean values observed in 36 healthy residents of Lima at sea level; in 34 healthy native residents of Morococha at 14,900 feet of altitude; and in three cases of chronic mountain sickness, also studied in Morococha. Points R, R' and R" correspond to the resting ventilation breathing air; the rest of the curves were constructed with values obtained at three-minute intervals during the CO_2 breathing. The alveolar air was continuously collected and analyzed with a Cambridge CO_2-analyzer.

It is not well understood why obese patients may underventilate at times. One of the theories [13] assumes that the increased work of breathing, a result of the weight abnormality, leads mechanically to the decrease in ventilation. This mechanism cannot be applied to our high-altitude patients. Obesity is almost absent in the native residents, and practically all of them show a

low body weight/body height ratio compared to men living at sea level. We are inclined to believe that chemical alterations in the respiratory center may be responsible for the changes in sensitivity and function. The clinical symptomatology of patients with chronic mountain sickness is mainly of a

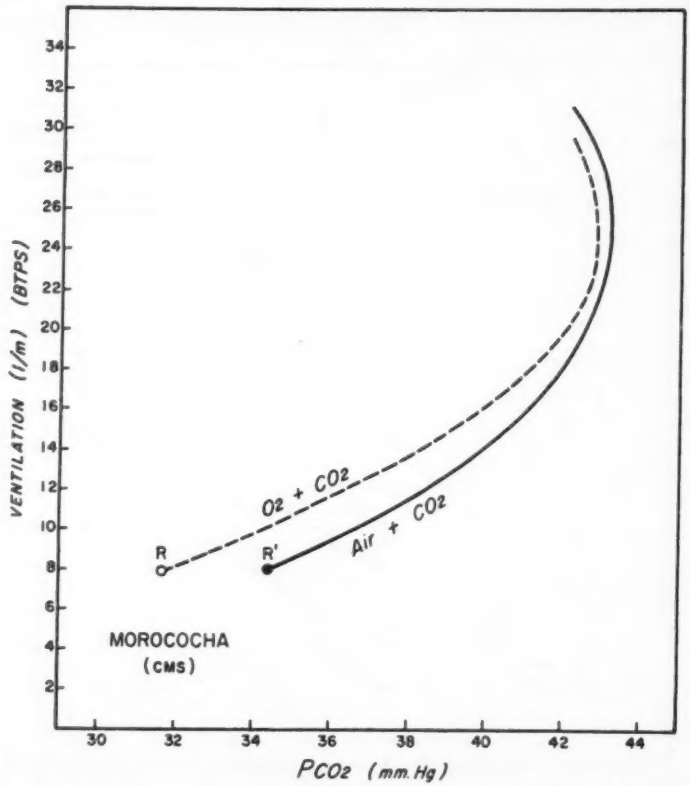

FIG. 5. Relationship between ventilation and alveolar pCO_2 in cases of chronic mountain sickness. One curve corresponds to breathing air and CO_2, and the other to breathing a 35% oxygen mixture with CO_2. Observations were carried out in Morococha at an altitude of 14,900 feet. R corresponds to the resting ventilation while breathing the 35% O_2 mixture, and R′ while breathing only air. (Curves constructed as explained in figure 4.)

nervous nature, which suggests a somewhat general disturbance of nerve function. The abnormal behavior of the center may represent one facet of such disturbance.

Acute pulmonary edema may develop on arrival at a high altitude. This is not frequently observed, but since it was first described in 1937,[14] a rather large group of cases has been reported by Lizárraga.[15, 16] An interesting feature is that all of the patients had been born at high altitudes, or had been

living for a prolonged time in the high environment, with no history of previous cardiac or respiratory symptomatology, and had developed the edema within the first few hours after returning to high altitudes, and after having been at sea level only a few days. In consequence, all had some degree of polycythemia associated with an increased blood volume in the lungs, and possibly a certain degree of hypertension in the pulmonary vascular bed. The exposure to an acute anoxia and low ambient pressure, under such circumstances, brought about the edema. A detailed study of these cases may prove useful in elucidating the still obscure pathogenic mechanisms of pulmonary edema in general. The administration of oxygen led to a complete recovery from symptoms in the cases observed at high altitudes.

One of the most interesting and perhaps most significant clinical aspects of permanent exposure to a high-altitude environment is the extremely low incidence of hypertension and symptoms dependent upon cardiovascular sclerotic processes. Peripheral blood pressures, at rest and during physical activity, have low values in healthy people of all ages, compared to those of the sea level population. From a total 2,206 patients hospitalized in the Chulec Hospital, a well organized and well equipped hospital in Oroya, a town located in the Andean region at an altitude of 3,370 meters (12,230 feet), only two (about 0.1%) were cases of hypertension. Coronary thrombosis and myocardial infarction also occur only very rarely. In three decades of personal experience at high altitudes, we have observed but one case of this nature in the population, which includes individuals of Indian as well as of several white races; and the medical centers located in these high zones have had a similar experience.

As to the possible factor or factors responsible for these peculiar characteristics of the high-altitude population, which are in contrast with the nature of the general morbidity and mortality rates in most parts of the world, we may mention that all of our investigations have shown a condition of greater vascularity and dilatation of the vascular bed in all organs, including the heart,[6] which suggests a low peripheral resistance. However, the degree to which sclerotic and degenerative processes in arteries and arterioles occur at high altitudes offers a very important and timely problem to be investigated. Some preliminary anatomic observations, which are being extended at the present time, seem to indicate a lower incidence of vascular sclerosis, in relation to age, at high altitudes. This study is being carried out in association with blood biochemical determinations considered to be significant in this respect. A small number of analyses of blood cholesterol in natives of Morococha have yielded values within normal limits.

In 1953 Alzamora and others [17] pointed out a higher incidence of patent ductus arteriosus in the native population of the Andean region in Peru. This finding, like the one obtained in the high plateau of Mexico,[18] has been repeatedly confirmed by studies in the high school population and by hospital

statistics.[19, 20] It is assumed that the hypoxia, which is originated by the decreased partial pressure of oxygen in the inspired air and which develops at birth and is permanent, and the presence of pulmonary hypertension, already mentioned, and which probably is also evident at that early age, are the factors mainly responsible for the higher incidence of patent ductus arteriosus at high altitudes. It is of interest that operative procedures being used to correct such anatomic abnormality carry a mortality risk no higher—and apparently even lower—than that observed at sea level.[21] This experience, and the analogous low mortality in general thoracic surgery,[22] (extensively carried out in hospitals located at altitudes of 4,330 meters (14,200 feet) and 3,730 meters (12,230 feet)) indicates the high degree of tolerance to hypoxic conditions shown by the native Indian population.

There are some other interesting features of medical practice at high altitudes which demand statistical studies and clinical investigation before final conclusions are reached, but preliminary observations justify a brief comment. There is a general feeling that the incidence of peptic ulcer [23] is greater at high altitudes, in spite of the fact that hypochlorhydria and achlorhydria are very frequent findings. This is interesting from the point of view of the apparently common association of peptic ulcer and polycythemia at sea level.

Liver disease, especially cholecystitis and cholelithiasis, is common in the high-altitude population, and calculi have been found to be of cholesterol composition in most cases. Surgeons are inclined to believe that keloid formation is a postoperative complication more commonly seen in high regions.

Finally, we may mention that there is not yet sufficient information regarding the comparative incidence of cancer and malignant processes at sea level and at high altitudes, with the exception of leukemic processes, which are very rarely found in Indian natives. Mori Chavez [24] has observed that experimental leukemia induced in susceptible animals has a lower rate of development at high altitudes.

In conclusion, we feel that a high-altitude population offers investigative possibilities as to two kinds of problems, closely related but not entirely similar. The first, which has been the more thoroughly explored but is not entirely solved, deals with the mechanisms responsible for the development of tolerance or acclimatization to hypoxia. The second is related to the effects of this condition when they are permanent in nature. This latter field of study may not only contribute to a better knowledge of living conditions in a low-pressure environment, but may also help in the better understanding of the clinical and physiopathologic processes frequently found at sea level.

Summario in Interlingua

Le studios e observationes del autor, facite principalmente in le Andes peruan a un altitude de 14.900 pedes, es le base de un description de certe alterationes functional e organic in subjectos acclimatisate in le curso de un longe periodo de sojorno in un ambiente de grande altitude.

Il ha essite demonstrate que subjectos san qui vive pemanentemente a grande altitudes ha moderate sed constante grados de hypertension pulmonar. Le registrationes electrocardiographic ab tal subjectos, mesmo in lor juventute, ha essite interpretate como reflectente hypertrophia dextero-ventricular, e iste supposition ha essite verificate per studios anatomic.

Multo interessante es le syndrome associate con le perdita del tolerantia pro un ambiente de basse pression. Isto ha essite designate como "chronic maladia del montanias." Le symptomatologia de iste condition es variabile, sed certe alterationes physiologic es demonstrabile in le majoritate del casos. Il occurre un augmento considerabile in le volumine de sanguine circulante, resultante integremente de un elevate componente cellular. Biopsias de medulla ossee revela hyperactivitate erythropoietic. Iste augmentate production de cellulas rubie es balanciate per un accelerate destruction cellular que se manifesta in le excretion de pigmento. Le nonsaturation oxygenic del sanguine arterial es marcate, con valores descendente usque a 60 o 70% pro oxyhemoglobina arterial. Le plus significative alteration respiratori es un hypoventilation relative. Le studios del autor indica alterationes in le responsa del centro respiratori al stimulation chimic. Le datos accumulate ha monstrate que in chronic maladia del montanias il occurre un reduction del responsa ventilatori al respiration de CO_2.

Es notate le occurrentia de acute edema pulmonar in monticolas qui—post breve periodos de sojorno a plus basse altitudes—retorna subitemente a lor previe habitat de grande altitude. Es etiam sublineate le importantia de un studio del incidentia relative de certe conditiones pathologic in habitantes de sitos de grande altitude in comparation con le incidentia del mesme conditiones in populationes normal al nivello del mar.

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ELECTROLYTE METABOLISM AND ALDOSTERONE SECRETION IN BENIGN AND MALIGNANT HYPERTENSION * †

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THE fundamental relationship between intravascular pressure and electrolyte metabolism is poorly understood. The hormones of the adrenal cortex which act to regulate sodium and potassium balance can produce hypertension both in man and in experimental animals.[1, 2] The hypertensive state produced by adrenal mineralocorticoids such as desoxycorticosterone is dependent upon administration of adequate amounts of sodium in the diet, whereas the hypertension induced by glucocorticoids such as hydrocortisone differs in that it is less severe, and it is not dependent upon sodium intake.[3]

Aldosterone, though more potent, produces effects on sodium and potassium metabolism similar to those of desoxycorticosterone. Aldosterone appears to participate in the regulation of arterial blood pressure. Patients with primary hyperaldosteronism uniformly exhibit hypertension, while, on the other hand, adrenalectomized subjects maintained on cortisone frequently exhibit an abnormally low blood pressure.

A number of observations have indicated a relationship between sodium balance and the blood pressure level of patients with hypertension. The beneficial effects of sodium deprivation and of various diuretic agents in hypertensive patients are well known. Furthermore, other studies have suggested that abnormalities in the tissue content of sodium and potassium occur in hypertensive patients.[4]

Previous investigations of the role of the mineral hormone, aldosterone, in hypertensive disease have yielded inconclusive results.[5] In the present study a method devised in our laboratory has been utilized to measure the amount of aldosterone actually secreted by the adrenal glands.[6, 7] This method obviates a difficulty inherent in studies which have been based on measurement of the small fraction of aldosterone excreted unchanged in urine. The new technic involves the injection of a tracer of tritium-labeled aldosterone

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and the determination of the specific activity of tetrahydroaldosterone in the subsequent 24-hour urine. The difference between the specific activity of the injected tracer and that of the urinary metabolite is a measure of the endogenous contribution, and, as such, permits estimation of the daily secretion. By this technic, normal subjects produce 150 to 350 μg. of aldosterone per day, and this value may rise to 1,000 μg./day with sodium deprivation. On the other hand, the feeding of excessive sodium can suppress the normal aldosterone secretion to as low as 50 μg./day.

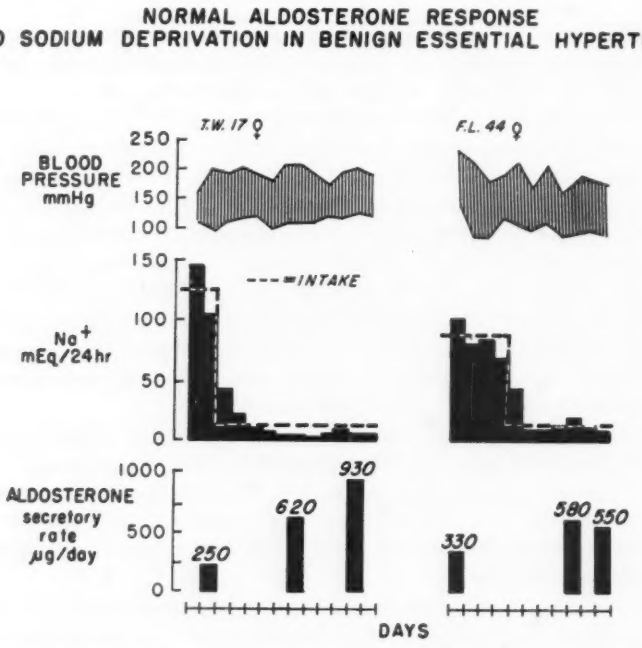

FIG. 1. Normal aldosterone response to sodium deprivation in primary (benign essential) hypertension. Metabolic balance data from two subjects with benign hypertension are presented. On normal intakes of sodium, both of these subjects exhibited normal secretion rates of aldosterone. Furthermore, both exhibited a normal response to sodium deprivation, characterized by prompt reduction in urinary sodium excretion. As a part of this physiologic response to sodium deprivation, the aldosterone secretion rate increased considerably in both patients. This response is similar to that observed in normal subjects.

This technic has been applied to the study of patients with arterial hypertension.[7] Changes in aldosterone secretion have been related to changes in electrolyte balance, and, when possible, to changes in the adrenal morphology. Our hypertensive patients have been simply classified into three groups. The first group, labeled primary hypertension, represents patients with benign essential hypertension. The second group, labeled advanced hypertension, includes those hypertensive patients with either nitrogen retention

or retinal hemorrhages, or both; and the third group, labeled malignant hypertension, comprises those patients with accelerated hypertension characterized by papilledema.

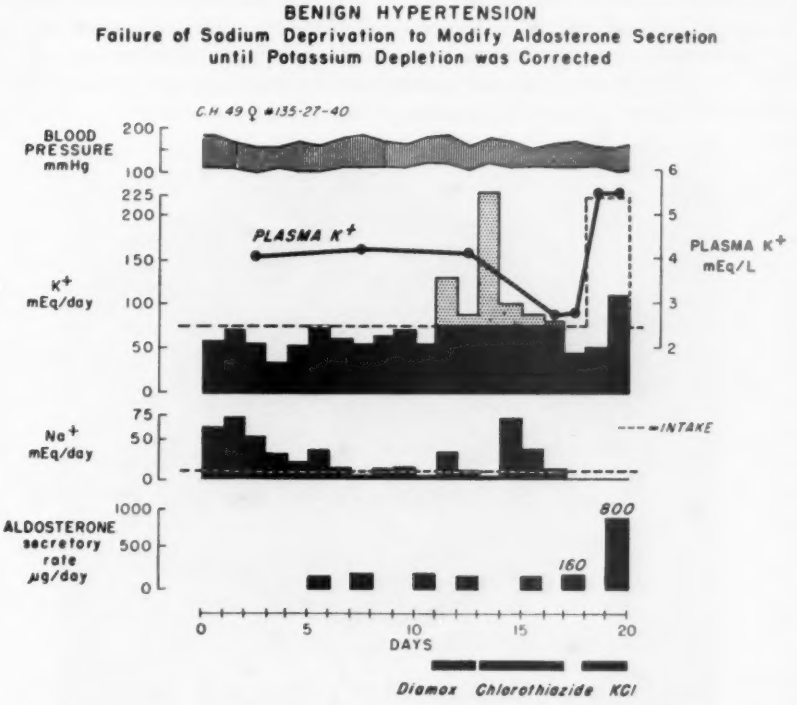

FIG. 2. Benign Hypertension. Failure of sodium depletion to modify aldosterone secretory rate until potassium was administered. This patient with benign hypertension on a constant diet gradually shut off sodium excretion in response to a reduced intake of sodium, but this response occurred in this subject without any significant change in aldosterone secretion. Sodium depletion was intensified by the use of acetazoleamide and chlorothiazide, but even then, aldosterone did not increase. These diuretic agents also produced potassium depletion with hypokalemia. When potassium was administered, the plasma K^+ rose sharply, as did the aldosterone secretion rate. This response is also similar to that of normal subjects (figure 1). The data illustrate that sodium conservation can occur without a rise in aldosterone secretion. Also, the data indicate that the state of potassium balance (and/or the plasma potassium) is an important stimulus to aldosterone secretion. A potassium change might often account for the increased secretion attributed to sodium or volume change.[8]

We began our work with a study of electrolyte and aldosterone metabolism in patients with benign hypertension. Figure 1 presents data taken from controlled metabolic balance studies of two subjects with benign hypertension. On normal intakes of sodium, both of these subjects exhibited normal secretion rates of aldosterone of 250 and 330 µg./day. Furthermore, both exhibited a normal response to sodium deprivation, characterized

by prompt reduction in renal sodium excretion. As a part of this physiologic response to sodium deprivation, the aldosterone secretion rate was shown to increase considerably (up to levels of from 580 to 930 μg./day). This response is entirely similar to the response we have found in normal subjects [6] under these circumstances, and therefore affords no evidence for an abnormality in aldosterone metabolism in benign hypertension. It is also of note that no significant changes in the arterial blood pressure were observed in association with the change in aldosterone secretion.

FIG. 3. Left adrenal gland from case 1. This gland weighed 10 gm., which is above the normal limits (table 2). The gland was rich in lipid and intensely orange-yellow in color. The cut surface revealed the cortex to be convoluted. Microscopic examination revealed moderate nodular hyperplasia. As with the other glands studied, it was not possible to define any specific zonation in the hyperplasia. No adenomata were found in any of the six cases reported here.

Earlier studies from our laboratory had suggested that the level of the plasma potassium ion might be an important stimulus, direct or indirect, to aldosterone secretion.[8] For a time this finding was not entirely accepted, but recently, with the use of our new method, the effect of potassium has been amply confirmed in normal subjects. Patients with benign hypertension also resemble normal subjects in this regard, as shown in figure 2. Here data are presented from a 49 year old woman with benign hypertension. It can be seen that this patient gradually shut off renal sodium excretion in response to a reduced intake, but this occurred in this case without a rise in aldosterone secretion. Sodium depletion was then intensified by the use

of Diamox, and later by chlorothiazide, but even so, aldosterone secretion did not increase. However, it should be noted that these diuretics also produced a negative potassium balance and hypokalemia, and this perhaps prevented the aldosterone rise. In support of this idea, when potassium was administered, the plasma potassium values rose sharply, and the aldosterone secretion rate also rose promptly (from 160 to 880 μg./day). These data illustrate that, in patients with benign hypertension (as in normal subjects), increased aldosterone secretion is not necessary for normal sodium conservation. But the plasma potassium and/or the state of potassium balance looms as an important stimulus to aldosterone secretion, and might often account for the increased secretion ascribed to sodium and/or volume changes. However, the patients with benign hypertension also seem similar to normal subjects with respect to their response to potassium administration.

TABLE 1

Clinical Features of Six Fatal Cases of Malignant Hypertension

Case	Age, Sex	Degree and Duration of Hypertension	Blood					Urine	
			Na mEq./L.	K mEq./L.	HCO_3 mEq./L.	Cl mEq./L.	Urea mg. %	Volume ml./day	Na mEq./L. day
1	57M	250/150 20 yrs.	138	3.2	34	92	40	3,300	79
2	48M	280/160 3 yrs.	135	3.7	26	95	71	3,040	53
3	53M	220/130 4 yrs.	132	3.6	30	92	37	1,920	101
4	42F	250/160 5 yrs.	140	4.1	27	95	45	1,500	43
5	44F	250/150 15 yrs.	141	3.2	28	101	47	1,400	51
6	46F	250/160 12 yrs.	126	3.9	27	80	78	1,600	42

As a consequence of these results, our interest in the possible role of aldosterone in hypertensive disease was dampened. But then we were presented with the case of a 57 year old man with a 20-year history of severe hypertension who, in the two years prior to study, had developed muscular weakness, episodes of nausea, slight polyuria and papilledema. This man presented azotemia (blood urea nitrogen, 40 mg.%). He repeatedly exhibited plasma potassium levels in the range of 3.0 mEq/L., with bicarbonate values usually above 30 mM/L. He was found to have hypersecretion of aldosterone, but no other evidence of adrenal hyperfunction. Because a tumor was not found, bilateral adrenalectomy in two stages was carried out. The adrenal glands in this patient were above normal in weight, and demonstrated increased nodularity and lipid deposits, as shown in figure 3. Unfortunately, shortly after surgery the patient developed terminal uremia. Postmortem examination confirmed the presence of necrotizing arteritis.

This experience called our attention for the first time to a possible relationship between aldosterone secretion and the disease known as malignant hypertension. At first, we regarded the finding of hypokalemic alkalosis in the face of the renal failure of malignant hypertension as an unusual happenstance, even though a review of the literature did reveal a few isolated case reports with similar electrolyte abnormalities.[9-11] But, in the ensuing year, we studied 20 additional patients with malignant hypertension, and, as will be seen, these patients have all shown a striking resemblance to our first case, not only with respect to the clinical findings, but also in their physiologic and pathologic abnormalities.

TABLE 2

Aldosterone Secretion and Morphologic Findings in Six Fatal Cases of Malignant Hypertension

Case	Aldosterone Secretory Rate μg./day (Normal Range 150 to 375)	Renal Pathology (+ to 4+)	Adrenal Weight* gm. (Normal Range 12.1±2.7, Septic Range 16.6±4.0)
1	600	++ Necrotizing arteritis	16.5
2	860	+++ Intimal sclerosis, but no necrosis	27.0
3	1,220	+ Necrotizing arteritis	17.0
4	2,180	+ Necrotizing arteritis	15.0
5	2,730	+ Necrotizing arteritis	17.5
6	10,000	+ Necrotizing arteritis	12.5
			(17.8) ave.

* Control adrenal weights (both glands) as determined in autopsy population at Presbyterian Hospital, New York City:

34 normal specimens	12.1 ± 2.7 gm.
21 subjects with septic illness	16.6 ± 4.5 gm.
25 subjects with benign hypertension	13.0 ± 2.6 gm.
5 subjects with renal hypertension	11.8 ± 2.1 gm.

All of the specimens of the adrenal glands described above exhibited moderate degrees of hyperplasia, slight nodularity and increased lipid. However, there was no definitive zonation noted.

Table 1 summarizes the clinical features of six fatal cases of malignant hypertension. These six patients all had severe hypertension, with the diastolic pressure ranging upwards from 130 mm. The known duration of the hypertension ranged from three to 20 years. At the time of our study, all six manifested nitrogen retention (blood urea nitrogen ranging from 40 to 90 mg.%). Despite renal failure, the plasma potassium tended to be low, with five of the six patients exhibiting values under 4.0 mEq./L. The plasma bicarbonate, often depressed in other forms of renal failure, tended to be high. These patients all had normal or slightly high urine volumes, but overt polyuria was present in only two of the six. The urinary sodium excretions are presented merely to indicate that a state of sodium retention did not exist at the time of study.

In table 2 the aldosterone secretion rates encountered in these same six patients with malignant hypertension are presented, along with a summary of subsequently obtained autopsy findings. Marked hypersecretion of aldosterone was demonstrated in all six of these patients, with the values ranging from 600 to 10,000 μg./day. All but one had overt necrotizing arteritis. However, the necrotic process was in no instance severe, and in some was minimal. The adrenal glands in all six cases were at or slightly above the upper limits of normal in weight. All of the glands revealed

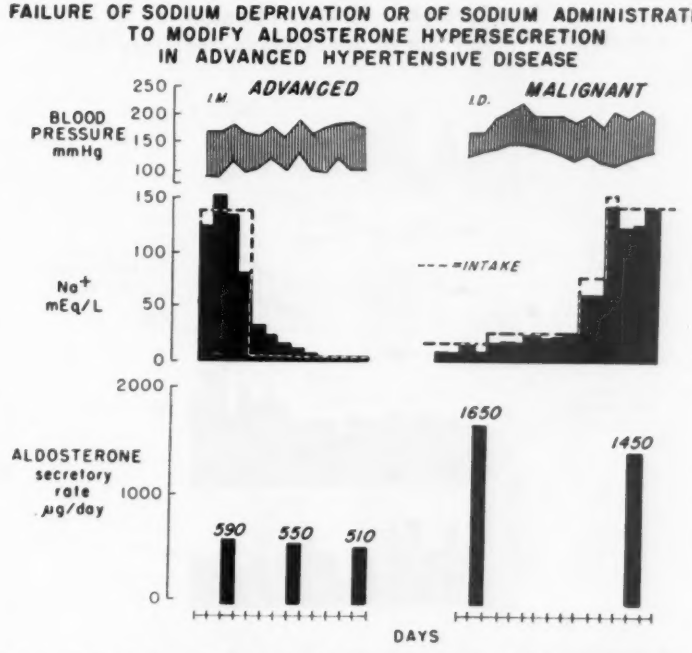

FIG. 4. Failure of sodium deprivation or of sodium administration to modify the aldosterone hypersecretion of advanced hypertensive disease. Under controlled metabolic conditions, neither sodium deprivation nor sodium administration resulted in any significant change in the abnormally high aldosterone secretion rate found in two subjects with advanced hypertensive disease. These findings are in contrast to those found in normal subjects and in subjects with benign hypertension (figure 1).

moderate bilateral (often nodular) hyperplasia with increased lipid. Thus, these patients differ from patients with primary aldosteronism [12] not only in their clinical features but also in that in no instance has an adrenal adenoma been found. The hypersecretion of aldosterone here appears to be the result of bilateral adrenal hyperfunction. It is of interest that, in five of six reported cases of Conn's syndrome "due to bilateral hyperplasia," malignant hypertension with papilledema was present.[13-18]

An effort has been made to characterize further the nature of the hypersecretion of aldosterone associated with malignant hypertension. In figure 4 data are presented from two metabolic balance studies of patients with severe hypertension. It can be seen that, in both instances, hypersecretion of aldosterone could not be modified significantly either by reducing or by increasing the sodium intake. Thus, in marked contrast to what is found in normal subjects and in patients with benign hypertensive disease, the secretion rate of aldosterone could not be modified by changes in sodium

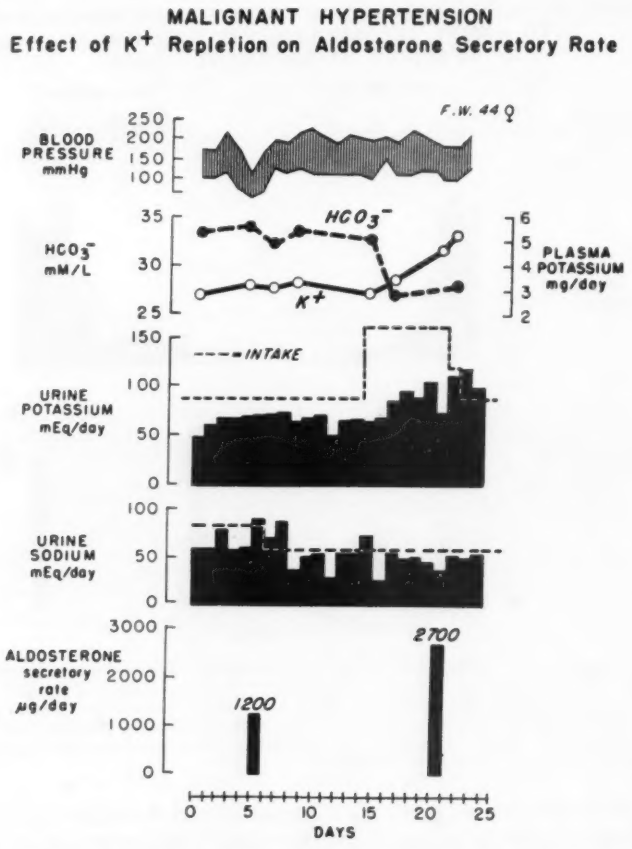

FIG. 5. Effect of potassium repletion on the aldosterone secretion rate in malignant hypertension. This 44 year old woman (case 5) received a constant, but unrestricted, intake of sodium and potassium. Marked hypersecretion of aldosterone was demonstrated. When the potassium intake was increased, the plasma K^+ rose from 2.9 to 5.5 mEq./L., and the plasma HCO_3^- fell from 33 to 27 mM/L. With potassium administration, the aldosterone secretion rate rose from 1,200 to 2,700 µg. Aldosterone metabolism in malignant hypertension thus resembles that of normal subjects with respect to the response to potassium administration.

intake. Of course, it is possible that, with more prolonged or intensive changes in sodium intake, the hypersecretion could be modified. Yet these data suggest a fundamental difference in the nature of aldosterone metabolism in malignant hypertension.

In figure 5, metabolic balance data from another patient with malignant hypertension are presented. While on a constant, but unrestricted, intake

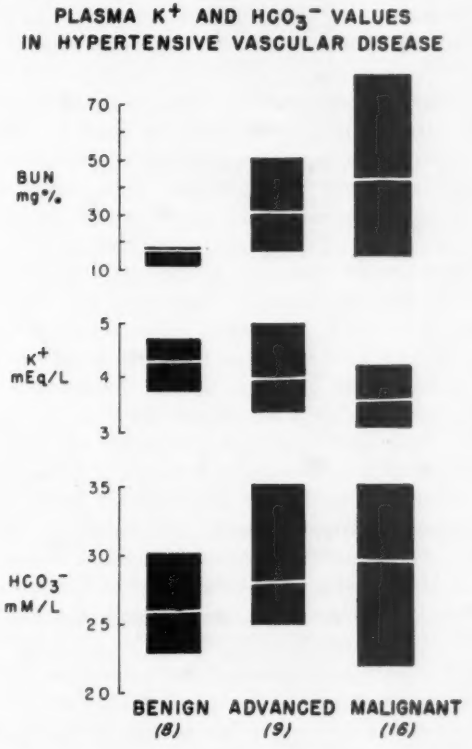

FIG. 6. The average values and the ranges of the plasma potassium and bicarbonate are presented for three groups of hypertensive patients. In eight patients with benign hypertension the average values were: K^+, 4.3; HCO_3^-, 26; urea, 17. In nine subjects with advanced hypertension: K^+, 4.0; HCO_3^-, 28; urea, 31. In 16 cases of malignant hypertension: K^+, 3.6; HCO_3^-, 29; urea, 43. The results obtained in malignant hypertension indicate a tendency to hypokalemic alkalosis. The values may have added significance since, in the presence of renal failure, anion retention usually tends to lower the plasma bicarbonate.

of sodium and potassium, marked hypersecretion of aldosterone was demonstrated (secretory rate of 1,200 μg.). Potassium repletion was then accomplished by the feeding of 162 mEq. of potassium daily. The plasma potassium rose from 2.9 to 5.5 mEq./L., and the plasma bicarbonate was

reduced to normal. In association with this potassium chloride administration, the aldosterone secretory rate rose from 1,200 to 2,700 μg./day. Thus, aldosterone metabolism in malignant hypertension seems to resemble that found in normal subjects in that the rate of secretion can be modified by a change in potassium balance (and/or by a change in the plasma potassium level). It perhaps should be noted in passing that potassium repletion in patients with malignant hypertension has been characteristically easy to accomplish. This perhaps is also different from what is found in benign primary aldosteronism, where potassium repletion may be quite difficult to achieve.

Aldosterone, when present in excess, characteristically leads not only to hypertension but also to potassium depletion and to abnormal sodium retention.[20, 21] If this hormone plays a part in the pathogenesis of malignant hypertension, then one might expect to find these other evidences of its biologic action. Figure 6 presents the averages and the ranges of plasma potassium and bicarbonate values found in patients with benign, advanced and malignant hypertensive disease. In benign hypertension these electrolytes were normal, with the plasma K^+ averaging 4.3 mEq./L., and HCO_3^- averaging 26 mEq./L. But in 16 cases of malignant hypertension the values appear to differ appreciably from those found in benign hypertension. In malignant hypertension the average plasma potassium value was 3.6 mEq./L., and the average plasma bicarbonate level was 29 mEq./L. These abnormalities may have additional significance because they were obtained in a group of patients with an average blood urea of 43 mg.%. Ordinarily, with such renal failure, retention of fixed anions tends to lower plasma bicarbonate and to raise plasma potassium (so-called renal acidosis). Notwithstanding this, abnormalities in plasma potassium and bicarbonate seem to remain a reasonably good guide to the presence of aldosteronism. It is of interest that similar abnormalities of plasma electrolytes in hypertensive disease have been commented upon by others.[22]

In figure 7 our experience in the study of patients with various types of hypertensive vascular disease is summarized. The adrenal secretory rates for aldosterone are shown on the top line in micrograms per 24 hours, and just below, the urinary sodium content for the corresponding 24-hour urine is presented. It can be seen that, in benign hypertension, the secretion rate of aldosterone falls in a range of from 180 to 330 μg./day, values similar to those found in normal subjects. In addition, two patients with hypertension due to unilateral renal disease have been found to have normal aldosterone secretion.

Marked hypersecretion of aldosterone was demonstrated in five cases of primary aldosteronism due to an adrenal adenoma, with the values ranging from 510 to 1690 μg./day. However, as can be seen, 14 of 15 patients with malignant hypertension who were studied manifested the most severe degree of hypersecretion, with the values ranging upwards from 510 to as high as

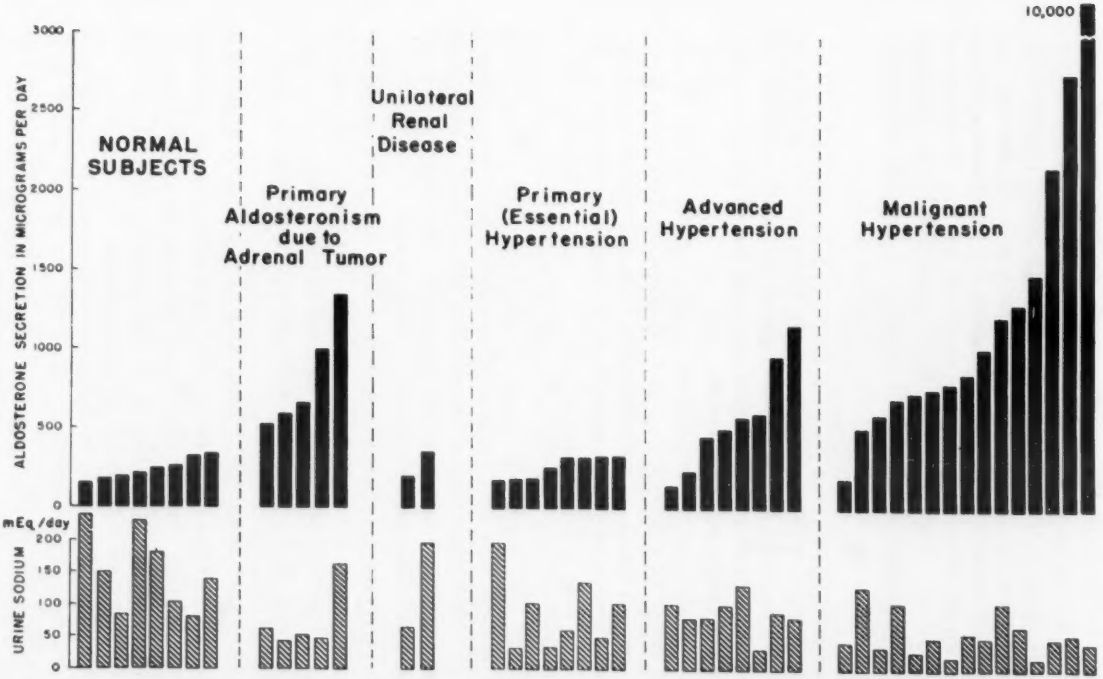

FIG. 7. The adrenal secretion rates of aldosterone in micrograms per 24 hours are presented for eight normal subjects, eight patients with primary hypertension, eight patients with primary hypertension with complications ("advanced" hypertension) and 15 patients with malignant hypertension. For comparative purposes, two patients with unilateral renal disease and five patients with primary aldosteronism are presented. The urine sodium content of the corresponding 24-hour urine collection is also shown. There is no evident hypersecretion of aldosterone in primary hypertension. In malignant hypertension, marked hypersecretion of aldosterone was found, and the values were often higher than those encountered in patients with primary aldosteronism. The patients with malignant hypertension resembled those with primary aldosteronism in that the hypersecretion was not associated with grossly reduced sodium excretion.

(Reprinted by permission from Laragh et al., J. Clin. Investigation, July, 1960.[7])

10,000 μg./day. Only once was the aldosterone secretion rate found to be normal in this disease, and in this one patient the subsequent course suggests that, at the time of study, the malignant state had been arrested.

From the data assembled on this chart it seems that aldosterone hypersecretion plays no part in the causation of simple primary hypertension. However, the data raise the question of whether aldosterone hypersecretion, perhaps when superimposed upon various underlying hypertensive states, might then participate specifically in the causation of the syndrome of malignant hypertension. Viewed in this light, aldosterone hypersecretion occurring in a hypertensive subject could initiate the development of the malignant state.

Summary

A precise technic of isotope dilution which measures the amount of aldosterone actually secreted by the adrenal glands has been employed to study the relationships between aldosterone secretion and electrolyte metabolism in benign and malignant hypertension.

In benign essential hypertension the adrenal secretion rate of aldosterone and the adrenal secretory response to sodium deprivation have been found to be within the normal limits. Furthermore, in these patients, as in normal subjects, the aldosterone response to sodium deprivation appears to be dependent upon the state of potassium balance.

The data obtained indicate that the syndrome of malignant hypertension is usually associated with hypersecretion of aldosterone. The patients with malignant hypertension who were studied differed from those with primary aldosteronism not only in their clinical features, but also in that, in malignant hypertension, the increased secretion of aldosterone was associated with bilateral adrenal hyperplasia rather than with an adenoma.

In addition to severe hypertension with vascular and renal complications, patients with malignant hypertension exhibit changes in their plasma electrolytes suggestive of aldosteronism. In 13 of 15 cases a tendency to hypokalemia or elevation of the plasma bicarbonate was encountered, even in the presence of renal failure.

In malignant hypertension, aldosterone metabolism also differs from that of normal subjects in that the secretion rate of aldosterone is not modified by changing the sodium intake. However, aldosterone metabolism in malignant hypertension resembles that in normal subjects in that the rate of secretion of the hormone is related to potassium balance.

Hypersecretion of aldosterone in malignant hypertension could be a secondary or concomitant phenomenon. However, the results which have been obtained make it reasonable to consider the possibility that hypersecretion of aldosterone plays a causal role in malignant hypertension.

This finding of a consistently increased aldosterone secretion rate in a disease where renal damage appears to be of primary importance perhaps suggests the existence of a renal factor, possibly angiotensin, which is involved in the control of aldosterone secretion.

ACKNOWLEDGMENT

The pathologic data in table 2 were kindly provided by Dr. Fred Lucas and Mr. John Sheagren.

SUMMARIO IN INTERLINGUA

Un precise technica de dilution de isotopos, mesurante le quantitate de aldosterona de facto secernite per le glandulas adrenal, esseva usate pro studiar le relation inter le secretion de aldosterona e le metabolismo de electrolytos in hypertension benigne e maligne.

In benigne hypertension essential, il esseva trovate que le prorata del secretion adrenal de aldosterona e le responsa del secretion adrenal a privation de natrium se tene intra le limites del norma. In plus, in iste patientes—como in subjectos normal—le responsa de aldosterona a privation de natrium pare depender del stato del balancia de kalium.

Le datos obtenite indica que le syndrome de hypertension maligne es usualmente associate con hypersecretion de aldosterona. Inter le patientes in le presente studio, illes con hypertension maligne differe ab illes con aldosteronismo primari non solmente in lor aspectos clinic sed etiam in le facto que in hypertension maligne le augmentate secretion de aldosterona es associate con bilateral hyperplasia adrenal plus tosto que con un adenoma.

A parte lor hypertension sever associate con complicationes vascular e renal, le patientes con hypertension maligne exhibi alterationes in lor electrolytos plasmatic que suggere le presentia de aldosteronismo. Hypokaliemia o elevation del bicarbonato del plasma esseva incontrate con surprendente frequentia, mesmo in le presentia de insufficientia renal.

In hyptertension maligne, le metabolismo de aldosterona differe ab illo de subjectos normal in que le prorata del secretion de aldosterona non es modificate per alterar le ingestion de natrium. Tamen, le metabolismo de aldosterona in hypertension maligne resimila illo de subjectos normal in le facto que le prorata del secretion de ille hormon es relationate al balancia de kalium.

Il es possibile que le hypersecretion de aldosterona in hypertension maligne es un phenomeno secundari. Illo etiam pote esser un phenomeno concomitante. In despecto de isto, le resultatos obtenite rende plausibile le possibilitate que hypersecretion de aldosterona ha un rolo causal in hypertension maligne.

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A CLINICAL STUDY OF THE CHRONIC LUNG DISEASE DUE TO NONPHOTOCHROMOGENIC ACID-FAST BACILLI * †

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Before the development of cultural methods, the diagnosis of tuberculosis was based upon the finding of acid-fast bacilli on microscopic examination, positive tuberculin skin test, and characteristic x-ray and histologic changes. It is now recognized that all of these findings may be present in other chronic lung infections. The clinical entity of such diseases produced by acid-fast bacilli other than the tubercle bacillus has assumed increasing importance recently, although it has been reported sporadically for many years.[1-14] The internist is confronted more frequently now with chronic pulmonary disease due to atypical mycobacteria.

Various bacteriologic methods have resulted in the identification of a group of mycobacteria capable of producing chronic pulmonary disease which are as yet unclassified,[15] having been described by some authors as atypical [1] or anonymous.[16] Runyon [16] has divided these organisms into three groups, according to photochromogenicity: (1) photochromogens, recently given the generic name of *Mycobacterium Kansasaii*, which are white or buff-colored in the dark, and develop a bright yellow pigment on exposure to light; (2) scotochromogens, which produce a yellow-orange pigment in the dark but develop a reddish color in the light; (3) nonphotochromogens, which we have divided into groups III-A (nonpigmented) and III-B (pigmented) (colonies of III-A organisms are white, buff or pale yellow, whereas those of III-B are pale orange; both, however, are unaffected by light); and (4) rapid growers, which will grow luxuriantly within three days.

More than 600 individuals in Florida have had atypical acid-fast organisms isolated from their sputum during a five-year period.[12, 13, 14] This report describes 116 cases who had multiple isolations of nonphotochromogens and who have completed a period of hospitalization.

As a group, these atypical mycobacteria differ from *Mycobacterium tuberculosis* in their ability to grow at room temperature. They differ from the tubercle bacillus also in their increased catalase activity, niacin negativity, nonpathogenicity for the guinea pig, and resistance to most antimicrobials

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before therapy.[13, 14, 17] Certain characteristic bacteriologic traits suggest that there may be several different strains of mycobacteria capable of producing chronic lung infection in humans within the group classified as nonphotochromogens.[12, 16] Group III-A is distinguished from III-B because of the difference in pigmentation, and because some of the III-A organisms are pathogenic for mice, whereas none of the III-B group studied demonstrated this pathogenicity. In addition, as a group the pigmented nonphotochromogens are characterized by a greater degree of susceptibility to most antimicrobials than are those in the III-A category. Several authors have reported resistance of these bacteria to the broad-spectrum antibiotics and to antifungal agents.[14, 17] In addition to being positive on culture, 70% of the sputum specimens were also positive for acid-fast bacilli on smear of concentrate. Search for other causative organisms in sputum, autopsy and surgical specimen was made in most cases. In 77 of the patients, cultures for fungi revealed only *Nocardia asteroides* in one instance and *Candida albicans* in a few cases. Culture for other organisms revealed none that is commonly considered pathogenic.

Epidemiologic studies have resulted in the finding of each atypical type, including Group III organisms, in the sputum or nasopharyngeal washings of healthy individuals with normal chest roentgenograms.[8, 15, 18] Comparative tuberculin skin testing, using antigen prepared from these atypical forms and standard tuberculin, has shown a higher incidence of reaction to specific tuberculin prepared from type III-A organism (the Battey strain) in the southeastern part of the United States,[19] which probably accounts for the increased incidence of nonspecific tuberculin reaction in this area.

Although most cases of nonphotochromogenic disease have been reported in the southeastern part of the United States (figure 1), infection with these bacilli is distributed widely throughout the world (figure 2). The reported incidence depends to a considerable degree upon the experience of laboratory personnel. We have written to the health departments of every State in the Union and to every country in the world and have received 150 replies. It was apparent that most laboratories recognized the obvious scotochromogenic (Group II) acid-fast bacilli and the photochromogenic (Group I) organisms. Many areas, however, were not aware of the existence of nonphotochromogenic infections. Recognition of these bacilli has been hindered by the fact that many laboratories still depend upon the smear alone for the diagnosis of tuberculosis. Significant numbers of cases of human disease due to nonphotochromogens have been identified in our country, and in Wales, the Netherlands, Spain, Romania, Malta, Australia and Jamaica. Isolated findings of pulmonary disease caused by these organisms have been reported also from Sweden, Finland, France, Switzerland, Peru and Canada. The nonphotochromogens are found primarily in the plains and in coastal or insular areas, with the notable exception of Zurich, Switzerland, and the State of Colorado.

Atypical mycobacteria have been isolated from the sputum of approximately 2% of admissions to tuberculosis hospitals in Florida [12, 13, 14] and Georgia.[10] Figure 3 shows the age, sex and race incidence of nonphoto-

FIG. 1. Geographic distribution of reported infections due to nonphotochromogens in continental U. S. A. (incomplete report).

FIG. 2. Geographic distribution of reported infections due to nonphotochromogens in the world (incomplete report).

chromogen disease which occurred predominantly in white males over 40 years of age. Approximately two thirds of the patients were from rural areas or small towns. Only 12 had a family history of tuberculosis, and

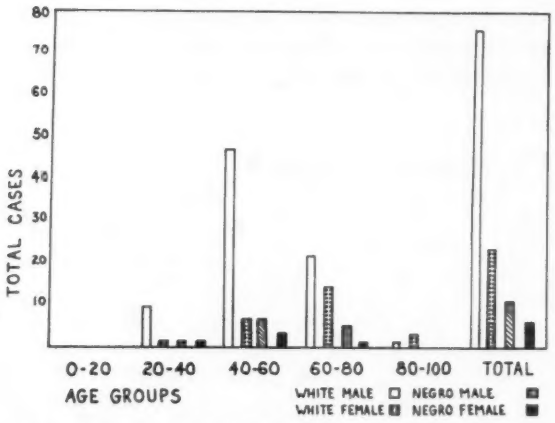

FIG. 3. Occurrence of nonphotochromogen disease by age, sex and race.

in no instance did nonphotochromogen infection occur in more than one member of a family.

The clinical symptoms of these patients were indistinguishable from those found in pulmonary tuberculosis. The onset in 87 was described as being of a chronic, insidious type; cough, weight loss and low grade fever were prominent symptoms. Hemoptysis also occurred in some cases. The extent of the disease was classified as far advanced in 52%, and as moderately advanced in all but six of the remainder. Cavitation was a prominent feature of the radiologic appearance, being present in 78% (table 1). Calcification was frequent, and pleural effusion occurred in four cases, one

TABLE 1

X-ray Characteristics and Classification on Admission

	III-A	III-B	Total
Minimal	5	1	6
Moderately advanced	45	4	49
Far advanced	56	5	61
Total	106	10	116
Cavity under 4 cm.	43	4	47
Cavity over 4 cm.	39	4	43
Total with cavity	82	8	90
Calcification	41	2	43
Pleural effusion	4*	0	4

* Pleural effusions were all class III-A. One had coexisting tuberculosis. Causative organisms were not isolated from the fluid in the four cases.

of whom had coexisting tuberculosis. The radiologic appearance of this disease could not be distinguished from that of tuberculosis.

Bronchoscopy was performed in 19 cases, 13 of whom had abnormal findings. Six of these exhibited only slight erythema, but the remainder showed more marked endobronchial pathology.

Tuberculin skin testing was not done in all patients, but comparative testing with PPD-S (standard tuberculin) and PPD-B (purified nonphotochromogen antigen) was done in 50 cases with multiple isolations of nonphotochromogens and 50 cases of proved tuberculosis. As shown in figure 4, there was generally a response to both antigens, but almost invariably there was a greater reaction to the homologous antigen.

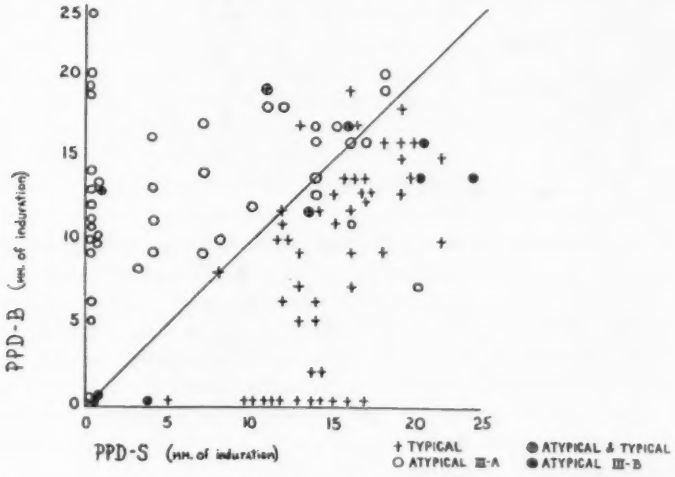

FIG. 4. PPD reaction in 100 patients—50 with tuberculosis and 50 with disease due to nonphotochromogens.

The incidence of associated disease was high in nonphotochromogenic infection, with an especially frequent occurrence of emphysema and tuberculosis (table 2). Comparison was made with 116 patients with tuberculosis matched as to sex, color and age by decade and, despite the fact that other disease was frequent in both groups, pulmonary emphysema occurred more often in the atypical group. The diagnosis of emphysema, however, was a clinical diagnosis, and was not confirmed by pulmonary function studies.

The response to therapy in the treatment of tuberculosis was superior to the response of infection due to nonphotochromogens. Because diagnosis was delayed by the necessity of awaiting culture reports, most patients were treated initially with isonicotinic acid hydrazide, para-aminosalicylic acid (PAS) and modified bed-rest. Patients were isolated as soon as the organisms were identified: in addition, at least two drugs were added, depending

TABLE 2

Comparison of 116 Cases of Nonphotochromogen Disease with 116 Cases of Pulmonary Tuberculosis of Similar Sex, Color and Age

Associated Diseases	Nonphotochromogens			Pulmonary Tuberculosis
	III-A	III-B	Total	
Pulmonary emphysema	34	1	35	9
Tuberculosis	18*	0	18	—
Atypical Mycobacterium isolated	—	—	—	2
Bronchial asthma	6	0	6	1
Bronchiectasis	6	0	6	1
Cor pulmonale	4	0	4	3
Primary carcinoma of lung	3	0	3	2
Silicosis	2	0	2	1
Hypertensive CV-renal disease	9	0	9	18
Peptic ulcer	3	0	3	3
Subtotal gastric resection	4	0	4	0
Diabetes	1	1	2	7
Hypopituitarism	2	0	2	0
Extrapulmonary carcinoma	4	0	4	3
Rheumatoid disease	5	0	5	1
Chronic alcoholism	4	2	6	6
No associated disease	47	6	53	68

* Three of these were questionable.

upon the susceptibility studies. Because of the delay in obtaining susceptibility data and the variable susceptibility pattern, random allocation to study the effect of a particular drug regimen was impossible. To date, therefore, we have been unable to prove a relationship between drug regimen, sputum conversion and x-ray improvement. Susceptibility studies initially demonstrate complete resistance to isonicotinic acid hydrazide and para-aminosalicylic acid, and a degree of susceptibility to streptomycin, cycloserine, viomycin, kanamycin and sulfisoxazole (table 3). There is also resistance to the broad-spectrum antibiotics.[14, 17]

TABLE 3

In Vitro Drug Susceptibilities of Group III-A and III-B Atypical Mycobacteria before Therapy

Drug	Conc. μg./ml.	Per Cent Susceptible	
		Group III-A	Group III-B
Isoniazid	1	1	15
PAS	10	3	15
Streptomycin	10	8	38
Cycloserine	20	35	46
Viomycin	10	1	12
Viomycin	100	33	80
Kanamycin	10	65	42
Sulfisoxazole	20	15	71
Amithiozone	10	8	30
Streptovaricin	1	41	15
Thiocarbanidin	1	7	0

TABLE 4

X-ray Response to Medical Treatment Alone

Response	III-A	III-B	Total
Slight or moderate improvement	24	2	26
Marked improvement	11*	2	13
No change	27	0	27
Worsening	12	0	12
Total	74	4	78
% Failure to improve	52.7	0.0	52.7

* Cavity closed on medical treatment alone in two cases.

Medical treatment alone is disappointing, since the x-rays of 52.7% of the patients had not improved at discharge when compared with the admission x-ray. In only two cases was cavity closure achieved without surgery (table 4). Treatment was also unsuccessful in many cases in converting sputum, and 43% of the discharged cases that were treated medically failed to attain sputum conversion.

Thirty-eight patients were subjected to major thoracic surgery (table 5). Thirty-seven had resection, and one had an extraperiosteal plombage. The major complications consisted of hemorrhage and bronchopleural fistulae,

TABLE 5

Results of Surgery in 38 Nonphotochromogens (32 III-A and 6 III-B): 37 Resections, 1 Extraperiosteal Plombage

		Segment	Lobe	Lobe and Segment	2 Lobes	Plombage	Total
Sputum Status							
Preop.	Pos.	6	12	4	2	0	24
	Neg.	1	8	3	1	1	14
Postop.	Pos.	2	4	1	2	0	9
	Neg.	5	16	6	1	1	29
Discharge	Pos.	1	3	0	1	0	5
	Neg.	6	16	7	2	1	32†
Total Cases		7	20	7	3	1	38
Complications							
BP fistula		2	0	1	0	0	3
Hemorrhage		2	0	0	0	0	2
Atelectasis		0	0	1	0	0	1
Cor pulmonale		1	0	0	0	0	1
Pneumonia		0	1	0	0	0	1
Deaths		1*	1†	0	0	0	2

* Died 27 months postoperatively.
† Died due to postoperative staphylococcal pneumonia.

TABLE 6

Bacteriology of Sputum and Resected Lung Tissues*

Preoperative Sputum		Lung Lesions	
Atypical Organism Isolated	Number of Patients	Number of Patients with Same Organism Isolated	Number of Patients with Negative Cultures
Group III-A	31	27	4
Group III-B	5	5	0
Totals	36	32	4

* Both Group III-A and III-B organisms were isolated from one patient's sputum. Only Group III-A organisms were isolated from lung lesions.

the latter being the most common (three patients). The complications, especially in those who had a segmental resection, appeared to be higher than would be expected in a comparable group of tuberculosis cases. A few of the patients required more than one resection and, despite this, two cases remained persistently positive. Two patients died, one of staphylococcal pneumonia in the immediate postoperative period, and one of cor pulmonale two years after surgery. A third patient, discharged with a normal chest x-ray and negative sputum, was re-admitted and died of rapidly progressive pulmonary tuberculosis. Table 6 shows that 32 of the 37 surgical specimens were positive culturally for organisms of the same type isolated from the sputum before surgery. Four, however, were negative. An additional patient had both III-A and III-B organisms isolated from the preoperative sputum, but the surgical specimen was positive for the III-A organism only.

TABLE 7

Fate of 116 Patients Infected with Nonphotochromogens

		Medical Rx		Surgical Rx		Total
		III-A	III-B	III-A	III-B	
Active		42	2	5	1	50
Positive	No cavity	9	1	5	0	15
	Cavity	17	0	0	0	17
Negative	Cavity	11	1	0	1	13
	X-ray change	5	0	0	0	5
Inactive		17	2	26	4*	49
Deceased		15	0	1	1	17
Total cases treated		74	4	32	6	116

* One patient died of fulminating tuberculosis on subsequent admission, 26 months after discharge.

Most of the specimens were inoculated into guinea pigs, with negative results. They were also negative for fungi and miscellaneous organisms.

Fifty patients were discharged with active pulmonary disease, the activity being based upon positive sputum in 32 cases, and upon residual cavity or x-ray change in the remainder (table 7). Forty-nine patients were discharged with inactive disease, 61% of these having received surgical treatment, and only 39% medical therapy alone. Seventeen patients died. Fifteen of the deaths had received medical treatment alone. Eleven of these were due to progressive pulmonary disease, associated in some instances with the development of superimposed bronchopneumonia and right heart failure. Seven had evidence of atypical infection only, and four were associated with concurrent pulmonary tuberculosis. Death was due to other causes in four instances, three as a result of carcinoma. Autopsy was done in eight cases and the specimen was cultured in four, with one negative and the others positive for organisms of the same type isolated from sputum before death. Pathologic study of surgical and autopsy specimens revealed changes characteristic of those seen in pulmonary tuberculosis.

Discussion

The members of the group reported in this paper were selected because of having had two or more isolations of nonphotochromogenic mycobacteria, usually over a considerable period of time. The frequent association with other diseases suggests the possibility that these microörganisms may produce disease more readily in such cases. The lack of a family history of disease caused by organisms of the same type, together with the observation that cross-infection with atypical mycobacteria in hospitalized patients has not occurred, implies that this is not a disease which is transmissible from one human to another.

The finding of these organisms in healthy individuals, together with the high incidence of skin sensitivity to the purified nonphotochromogen antigen, suggests that infection with this mycobacterium is rather common, even though the clinical disease is uncommon. *M. tuberculosis* is found more often in association with the single isolation of atypical mycobacteria than with multiple isolations,[14] and we are inclined to dismiss such solitary isolations as unimportant in most instances. We have, however, observed cases with abnormal chest x-ray and persistently negative sputum that have had a cutaneous reaction to PPD-B which was more strongly positive than the reaction to PPD-S, indicating that there was at least a possibility that previous infection with a nonphotochromogen organism accounted for the positive skin reaction and x-ray changes.

The unfavorable response to medical treatment may be accounted for in part by the age of the patient and the coexistence of other diseases, but the most apparent reason is the lack of effective antimicrobials. Surgical therapy was used in only a limited number of cases (32%) because of age,

pulmonary functional impairment and associated disease. Those treated in this manner, however, fared much better than did the patients treated medically, but complications occurred in a few, and failure to convert sputum was encountered in 13%.

Most cases unsuitable for surgery, whether the sputa were positive or not, had reached the point of maximal hospital benefit within a six- to nine-month period. We have discharged these patients customarily, and most have remained at home asymptomatic. We know of no instance in which they have transmitted this infection. Despite the use of antituberculosis drugs from the date of admission to the hospital, we believe that two patients have acquired infection with drug-resistant tubercle bacilli while hospitalized, and for this reason we consider isolation to be imperative, and feel that the patient must not be hospitalized beyond the point when maximal benefit of treatment has been obtained.

Summary

One hundred sixteen cases have been studied of chronic pulmonary disease due to nonphotochromogenic acid-fast bacilli similar to tuberculosis in clinical, radiologic and pathologic characteristics. The organism is differentiated from the tubercle bacillus by cultural methods and nonpathogenicity for the guinea pig. The disease is characterized by predominant occurrence in white males over 40, high incidence of associated disease, and no evidence of contagiousness. Patients reacted more strongly to the homologous antigen on skin test.

Response to medical therapy was poor as compared to that seen in the treatment of tuberculosis, with failure of x-ray improvement in 53%, and a 43% failure of sputum conversion. Response to surgery was more favorable, with sputum conversion in 87%. Seventeen patients died, 11 of progressive pulmonary disease. Two patients were re-admitted with pulmonary tuberculosis, and one of these died of rapidly progressive disease.

The following therapeutic program is recommended: (1) isolation from patients with tuberculosis on identification of the organism, or whenever skin test reaction to PPD-B is greater than to PPD-S; (2) early surgery in suitable cases; (3) prophylactic treatment with isoniazid, together with two additional drugs to which the organism has partial or complete susceptibility; (4) discharge as soon as maximal benefit of treatment has been achieved.

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Summario in Interlingua

Casos de chronic morbo pulmonar causate per atypic mycobacterios es uniformemente distinguibile ab illos causate per le bacillo de tuberculose human gratias al incapacitate de ille atypic mycobacterios de producer un morbo progressive in porcos de India e gratias, in plus, a plure proprietates bacteriologic de illos, incluse le tracto designate per Runyon como photochromogenicitate e usate per ille como base de un systema de classification. Runyon divide le organismos in question in quatro categorias: Gruppo I, le photochromogenos, que disveloppa un pigmento jalne post exposition al lumine; guppo II, le scotochromogenos, que produce un pigmento de color orange in le obscuro e deveni plus rubie in le lumine; gruppo III, le nonphotochromogenos, in que le lumine exerce nulle influentia; e gruppo IV, le crescitores rapide, que es capace a crescer intra tres dies.

Cento dece-sex casos de chronic infectiones pulmonar causate per nonphotochromogenos (con multiple isolationes) esseva studiate in hospitales pro tuberculose in Florida. Iste casos habeva manifestationes radiologic, pathologic, e clinic simile a a illos de tuberculose.

Le morbo predomina in masculos de racia blanc de plus que 40 annos de etate e es frequentemente associate con emphysema e tuberculose.

Un plus alte incidentia de sensibilitate cutanee al purificate antigeno preparate ab le nonphotochromogenos que al purificate derivato standard de proteina ha essite reportate in le sud-est del Statos Unite. Sensibilitate cutanee a antigeno nonphotochromogene es commun in juvene adultos, lo que suggere un alte frequentia del infection. Morbo de grado clinic es relativemente incommun: mycobacterios atypic es isolate ab solmente 2% del patientes admittite in hospitales pro tuberculose in Florida e Georgia. Approximativemente un medietate de iste casos ha mutiple isolationes de nonphotochromogenos. Nos ha nulle cognoscentia de un caso in que iste infection esseva transmittite ab un human a un altere.

Le radiographia obtenite al tempore del admission del patiente revelava moderate o avantiatissime grados del morbo in 95% del casos. Cavitation esseva presente in 78%. Le bronchoscopia esseva anormal in plure casos sporadic.

Le patientes esseva insulino-positive in le majoritate del casos. Le resultatos de tests cutanee in 50 patientes con morbo nonphotochromogene esseva comparate con le correspondente resultatos in 50 patientes con tuberculose. Esseva usate in iste tests standard derivato de proteina purificate e purificate antigeno nonphotochromogene. Con pauc exceptiones, le reaction esseva plus fortemente positive post le uso del antigeno homologe.

Studios de susceptibilitate ante le therapia revela que—reguardate como un gruppo—le nonphotochromogenos es resistente a isoniazido e acido para-aminosalicylic sed possede un certe grado de susceptibilitate a streptomycina, viomycina, cycloserina, e sulfisoxazol.

Le tractamento consisteva in le administration prophylactic de isoniazido, insimul con le uso del drogas indicate secundo le tests de susceptibilitate. Le tractamento non resultava in un melioration del radiogramma in 52, 7% del casos e non effectuava un conversion del sputo in 43%. Chirurgia thoracic esseva effectuate in 38 casos—resection in 37 e plombage extraperiosteal in le trenta-octave. Conversion del sputo occurreva in 87%.

Dece-septe patientes moriva, duo post le intervention chirurgic. Dece-un moriva de progressive morbo pulmonar. Quatro del mortes esseva associate con co-existente tuberculose. Quatro resultava de altere causas. Un patiente additional moriva de tuberculose fulminante al tempore de su re-hospitalisation subsequente.

Quaranta-novem patientes esseva dimittite ab le hospital con morbo inactive, 50 con morbo active. Le criterio pro activitate esseva le positive sputo in multe casos e alteration radiologic o cavitation residue in le resto.

Es recommendate que le patientes de iste typo es segregate intra le hospitales pro tuberculose, que illes es tractate con antimicrobiales (e chirurgia, si indicate), e que illes es dimittite si tosto que illes ha derivate le beneficio maximal ab lor hospitalisation.

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THE LIVER IN PORPHYRIA CUTANEA TARDA *

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THE porphyrias belong to the group of diseases that have been called inborn errors of metabolism. So-called congenital or erythropoietic [1] porphyria with severe light sensitivity is probably inherited as a recessive trait in man, and is certainly recessive in cattle.[2] Acute intermittent porphyria is a dominant character.[3, 4] Dean and Barnes [5, 6] in South Africa have reported a familial incidence of patients showing light sensitivity, together with abdominal symptoms and sometimes with neurologic lesions—a clinical picture similar to acute intermittent porphyria combined with light sensitivity. They have shown that this symptom complex is obviously inherited dominantly.

The present author (J.W.) coined the term porphyria cutanea tarda for patients with cutaneous symptoms occurring late in life. Recent investigations by one of us (B.H.) have shown that even completely healthy and seemingly normal family members may have a deranged porphyrin metabolism. The disease therefore probably also has a genetic background. On the other hand, Arzt and Tappeiner [7] in Vienna and Brunsting [8] at the Mayo Clinic, who have a wide experience, have stressed the importance of alcohol in the development of this disease. It is generally stated in the literature that these patients suffer from "liver cirrhosis." [9] Very few postmortem findings are available, and a thorough analysis of the clinical data from the published cases does not indicate severe liver injury. This could be explained in part by the fact that few observations were made by internists.

It is well known that Sweden has a comparatively high incidence of acute intermittent porphyria. (About 500 cases are known to us.) We have analyzed a great number of families with this disease, including one family with about 175 affected members, and have never found any members with light sensitivity. Congenital porphyria has never been described in Sweden. In only one patient that we have seen was the South African type of porphyria probably present, whereas typical porphyria cutanea tarda is not too rare in Sweden. Family studies have convinced us that these four different porphyrias represent different biochemical disturbances and have different clinical pictures. Each remains true to type, however. "Transitions" do not exist, as each disease is obviously caused by a specific mutation.

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The clinical and biochemical data regarding the type of liver injury reported in such patients are rather scarce, and we have therefore collected all available findings from patients observed by us, and from case histories put at our disposal by many colleagues in Sweden. (For this we offer our sincere thanks.)

It is of course important for the correct assessment of a patient with liver disease to analyze different partial functions of this organ. We have therefore divided the symptoms according to carbohydrate, protein, pigment, cholesterol and prothrombin metabolism and excretory capacity.

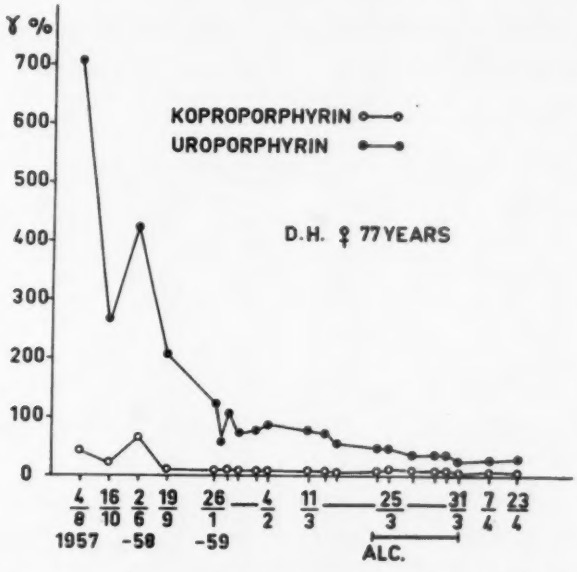

FIG. 1. Decreasing excretion of urinary uroporphyrin in case D.H. over a three-year period.

The carbohydrate metabolism as judged from galactose and glucose tolerance tests has always been normal in the cases examined. Cholesterol and prothrombin values have also been normal. Protein metabolism has been studied by electrophoresis in 11 cases. The γ-globulin was normal or borderline in all except four patients (G.A.♂, E.Ni., O.F., E.No.). Two of these patients (G.A.♂, E.No.) were rather severe alcoholics. The albumin was found to be really low in one elderly, possibly malnourished person (D.H.), and slightly decreased in two other cases (G.A.♂, S.L.). The thymol values were normal on the whole except in the patient with the highest γ-globulin (E.No.). It is therefore obvious that the metabolism of the serum proteins is usually not very much impaired in these patients.

In a disease with a basic disturbance of porphyrin metabolism, the condition regarding pyrrole-containing pigments seems to be of special interest. Many patients had slight or no excretion of urobilin and urobilinogen in the urine. It is also obvious that the capacity of the liver to excrete bilirubin is usually quite sufficient. Only two out of the 11 patients with determinations of serum bilirubin had pathologic retention (H.L., L.H.). The enzymes responsible for the passage of bilirubin into the bile therefore seem to be sufficient. Bilirubin loading tests were not performed because of the difficulties in obtaining the pure substance.

TABLE 1

Porphyria Cutanea Tarda: Liver Function

Case	Urobilinuria	Bil./s. mg./100 ml.	Thymol Ext. N.v. 0–0.11	El.-phoresis		BSP		P.A.D. Liver
				Alb. N.v. >4.2	γ N.v. <1.1	%	Year	
1. *H. B. ♀	(+)	0.3	0.03	4.8	1.3	16	1957	—
	Neg.	0.2	0.03	4.5	0.7	7	1958	
2. *D. H. ♀	(+)	0.5	0.06	3.0	1.2	37	1955	Incipient cirrhosis, red fluoresc.
	(+)	0.5	—	—	—	44	1956	
	(+)	0.5	0.03	3.0	1.4	41	1957	
	(+)	0.7	—	3.6	1.4	29	1959	
3. L. H. ♀	++	1.5	0.03	4.4	0.7	31		Steatosis, red fluoresc.
4. G. A. ♀	Neg.	—	<0.11	—	—	24		—
5. E. Ni. ♀	+++	—	1 U.	<4.4	>1.1	—		Normal
6. *G. A. ♂	Neg.	0.3	—	3.9	1.9	19		—
7. *G. H. ♂	+++	0.4	<0.11	—	—	—		Incipient cirrhosis
8. *E. J. ♂	(+)	0.7	0.08	Norm.	Norm.	—		Incipient cirrhosis
9. S. L. ♂	(+)	0.6	0.02	4.1	0.8	16		—
	—	—	—	—	—	10		
10. *H. L. ♂	++	1.5	0.08	4.8	1.1	25	1958	—
	—	1.1	0.09	5.0	0.9	—		
11. *E. No. ♂	(+)	—	0.16	4.9	2.8	—		Moderate cirrhosis
	—	—	0.12	—	—			
12. O. F. ♂	Neg.	0.3	0.08	4.3	1.7	20		—
13. *H. J. ♂	(+)	Norm.	Norm.	Norm.	Norm.	9.5		Fibrosis
14. *G. E. ♂	Neg.	0.9	1.7 U.	—	—	—		Incipient cirrhosis?

* Alcoholic.

This finding is in contrast to the regular occurrence of decreased bromsulfalein excretion in the active stage of the disease. The patient with the most severe disturbance (D.H.) (figure 1) did not improve her excretion very much in spite of the fact that her urinary uroporphyrin came down very definitely during the three years that we could observe her. At the same time, her cutaneous symptoms disappeared. We found two other patients (H.B., S.L.) in whom abstinence from alcohol gave marked improvement in bromsulfalein excretion, together with normalization of porphyrin metabolism and disappearance of cutaneous symptoms. Liver biopsies were

performed in eight cases, and slight cirrhosis or steatosis was noticed in seven of them. Findings indicating moderate cirrhosis were present in only one patient.

One of us has investigated the urine from 21 patients as to porphyrins and porphyrin precursors (tables 2 and 3). The methods used have been described earlier.[10] Porphobilinogen was always normal. In one patient (B.N.), δ-aminolevulic acid (ALA) was found in increased amounts on two occasions but was absent on two later examinations. In all others the ex-

TABLE 2

Porphyria Cutanea Tarda

Case	Age at Onset	Date	ALA mg. per 100 ml. N.v. < 0.6	PBG mg. per 100 ml. N.v. < 0.2	Uroporphyrin μg. per 1,000 ml. N.v. < 15	Coproporphyrin μg. per 1,000 ml. N.v. < 175
			Females			
1. B. N.	16	57 07	1.4	0.1	+++	+
		57 07	1.0	0.1	+++	+
		57 08	0.3	0.1	+	neg.
		57 10	0.3	0.2	11	108
2. M. P.†	10/12	58 01	0.3	0.1	7,272	895
3. B. P.†	2	58 01	0.2	0.1	4,040	250
4. A. S. P.†	9	57 07	0.2	0.1	++	+
		58 12	0.2	0.1		
5. D. H.*	72	57 04	0.1	0.1	+++	++
		57 10	0.3	0.2	2,674	231
		58 09	0.4	0.1	2,004	27
		59 03	0.2	0.1	34	7
6. H. B.*	55	57 09	0.3	0.1	2,457	544
		57 11	0.1	0.03	2,069	482
		58 03	0.3	0.2	1,868	322
		58 09	0.1	0.1	0	50
7. He. L.	51	58 10	0.03	0.1	1,578	409
8. L. H.	55	59 01	0.7	0.3	8,640	862
		59 02	0.4	0.2	8,242	1,106
		59 03	0.5	0.1	9,311	902
9. G. A.	62	59 02	0.2	0.1	5,050	591
10. E. N.	75	59 03	0.6	0.1	282	19

* Alcoholic.
† Probably South African type (M. P. and B. P. from Holland).

cretion of ALA was almost within normal limits. Uroporphyrin and coproporphyrin are definitely increased, with marked preponderance of the uroporphyrin. If a remission can be obtained, uroporphyrin values tend to come down (figure 1). The disturbance of pyrrole and porphyrin metabolism, and not just the clinical picture, is therefore fundamentally different from what we see in acute porphyria of the Swedish type, and also from the South African type. In several cases, fecal porphyrin was also markedly increased. The porphyrin data will be published in greater detail in a joint study with Dean and Barnes in South Africa.

If we assume that porphyria cutanea tarda is caused by an enzymatic block, as is the case with other inborn errors of metabolism, some hypotheses could be of interest. Recent biochemical investigations have shown that uroporphyrin III in its reduced form is obviously decarboxylated to coproporphyrinogen, and this is transformed to protoporphyrin. A block in this latter process could account for the primary increase in coproporphyrin and also through a negative feedback mechanism for the increase in the uroporphyrin. A block after this substance is also possible. The patients in remission, and also the clinically symptomless carriers of the trait, have

TABLE 3

Porphyria Cutanea Tarda

Case	Age at Onset	Date	ALA mg. per 100 ml. N.v. < 0.6	PBG mg. per 100 ml. N.v. < 0.2	Uroporphyrin µg. per 1,000 ml. N.v. < 15	Coproporphyrin µg. per 1,000 ml. N.v. < 175
			Males			
1. S. T.*	35	57 02	0.2	0.03	++	(+)
		58 09	0.4	0.3	0	25
2. O. G.*	42	57 09	0.4	0.1	3,145	466
		58 10	0.2	0.1		
3. H. J.*	54	57 09	0.3	0.1	1,360	483
		58 09	0.3	0.1	1,264	345
4. G. A.*	76	57 06	0.1	0.01	+++	+
		57 10	0.3	0.1	938	378
		58 03	0.1	0.1	1,903	228
		58 09	0.1	0.1	2,482	343
5. S. L.	45	57 08	0.6	0.1	++	Neg.
		57 09	0.3	0.2	875	105
		57 10	0.3	0.1	252	68
		58 09	0.4	0.1	1,161	85
6. G. H.*	54	58 10	0.1	0.1	65	16
7. Ho. L.*	41	58 06	0.1	0.03	315	105
		58 11	0.1	0.1	181	335
8. E. J.*	44	58 10	0.5	0.1	2,158	812
9. O. F.		58 11	0.1	0.04	3,053	418
10. E. No.*	45	58 11	0.2	0.2	3,380	692
11. G. E.*	48	58 12	0.3	0	781	64

* Alcoholic.

increased coproporphyrin excretion in the stools and only slight increase in urinary uroporphyrin. It was found by Hans Fischer that coproporphyrin was excreted through a normal liver into the bile, and that it disappeared from the body with the stools. During periods with cutaneous symptoms, uroporphyrin is obviously formed in increased amounts in patients with porphyria cutanea tarda. The serum is then fluorescent, the skin is photosensitized, and much uroporphyrin is found in the urine.

How could the deleterious influence of alcohol be explained? If the enzymes responsible for transformation of higher carboxylated porphyrins to protoporphyrin are supposed to be insufficient *and* alcohol-sensitive, this

could well be the explanation. Members of such families with only excess coproporphyrin in their stools probably pass unnoticed throughout their entire lives. If they start drinking, the biochemical balance is upset and clinical symptoms appear.[11] Primaquine and fava bean sensitivity may be quoted as a parallel mechanism. Erythrocytes having decreased activity of a specific—primaquine sensitive—enzyme, may function normally until the balance is upset by the administration of primaquine or by the ingestion of fava beans. Another similar example would be succinylcholine sensitivity from deficient function of the corresponding esterase. Both primaquine and succinylcholine sensitivities are inherited enzyme defects. An obvious parallel would also be the deleterious effects of barbiturates on patients with acute intermittent porphyria.

To my mind, the porphyrias represent interesting examples of hereditary enzyme defects with special sensitivity for toxic substances. The interrelation of genes-enzymes-toxic factors and metabolic disturbances with signs of auto-intoxication is well illustrated. Also, the mode of action of alcohol on liver cells could possibly be better understood by studies along similar lines. If the liver in porphyria cutanea tarda has only "one weak spot"—according to the theory, one gene, one enzyme—it may well be that the toxic influence of alcohol acts at this metabolic level. If this is the case, the interrelationship of several metabolic functions should be studied in such patients. Similar studies regarding alcohol dehydrogenase in common alcoholic cirrhosis would be of interest. The increased consciousness among clinicians of such monoenzymatic disturbances, both inherited and acquired, will probably lead to important advances in medical knowledge.

Summario in Interlingua

Le autores mentiona quatro typos de porphyria: (a) Porphyria congenite con sensibilitate a lumine; (b) acute porphyria intermittente; (c) acute porphyria intermittente con sensibilitate a lumine; e (d) porphyria cutanee tarde. Istos es reguardate como membros del gruppo de morbos designate como innate errores de metabolismo. Studios familial ha convincite le autores que iste differente porphyrias representa differente perturbationes biochimic e que cata un de illos es causate per un mutation specific e remane fidel a su typo.

Es presentate datos concernente le function hepatic in 14 casos de porphyria cutanee tarde. Le metabolismo de hydrato de carbon, de proteina, de cholesterol, de pigmento, e de prothrombina esseva essentialmente normal. Le function excretori—secundo tests a bromsulfaleina—se monstrava regularmente vitiate; e in septe inter octo casos in que biopsias hepatic esseva effectuate, leve grados de cirrhosis o de steatosis esseva constatate. In duo casos, abstinentia ab alcohol resultava in un melioration del excretion de bromsulfaleina e le disparition del manifestationes cutanee.

In 21 casos de porphyria cutanee tarde, le studio del porphyrinas e precursores de porphyrina revelava marcate augmentos del excretion de uroporphyrina e de coproporphyrina. Le autores suggere que un carentia enzymatic resulta possibilemente in un bloco in le transformation de coproporphyrinogeno in protoporphyrina. Le effecto adverse de alcohol consiste possibilemente in un aggravation del preexistente carentia enzymatic.

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THE OCCURRENCE OF INTRACELLULAR IRON IN GAUCHER'S DISEASE * †

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GAUCHER'S disease is a metabolic disorder characterized by the presence in various organs of large cells containing the cerebroside, kerasin.[1, 2] These cells are found in greatest number in the bone marrow, spleen, liver and lymph nodes,[3] structures which also contain the bulk of the reticuloendothelial cells of the body. The latter are believed to be the progenitors of Gaucher cells,[4-6] in addition to their other functions, which include a role in the metabolism and storage of iron.[7-12] Earlier papers have disagreed as to the distribution of tissue iron in this disorder; it has therefore been deemed worth while to reëxamine this problem, placing particular emphasis on the occurrence of visible iron within the pathognomonic cells.

MATERIALS AND METHODS

Five patients, three males and two females, ranging in age from eight to 52 years, were diagnosed as having Gaucher's disease on the basis of finding typical cells in bone marrow aspirates. All but one had splenomegaly, the spleens varying in size from being barely palpable to occupying almost half of the abdominal cavity. No gross hematologic abnormalities were present in three of the cases. However, one patient had a hemoglobin of 11.5 gm. per 100 ml., and another had a concomitant acute myelogenous leukemia.

Sternal marrow was obtained in the usual manner and ejected onto a glass slide from which the blood was decanted. Several smears were made from the remaining particles. In each case, some were stained with Jenner-Giemsa [13] and others with the Prussian blue technic of Rath and Finch,[14] employing 1% safranine as a counterstain. For comparison of marrow iron quantity and distribution, bone marrow aspirates were obtained from several normal individuals and from a patient having a chronic hemolytic anemia with transfusion siderosis.

RESULTS

In Jenner-Giemsa-stained smears (figure 1), Gaucher cells are seen to be large round or ovoid cells ranging from 30 to 80 micra in diameter.

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They usually contain one nucleus, but binucleated and multinucleated forms are not uncommon. The round or oval nucleus, which often has an irregular border, tends to be eccentric in position. It varies from one fourth to one sixth the diameter of the cell. Minute, apparently structureless areas

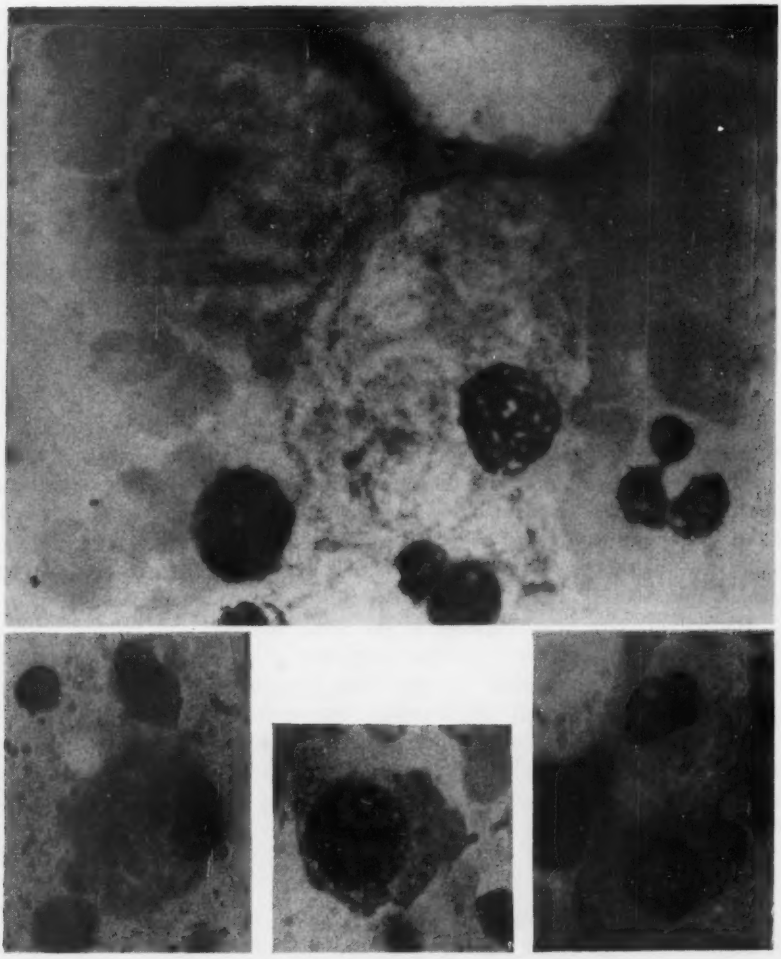

FIG. 1 (*above*). Gaucher cells (Jenner-Giemsa × 1200). (These photographs and those that follow are oil immersion views of bone marrow smears.)

FIG. 2 (*below, left*). Gaucher cell. Note phagocytized erythrocyte fragment next to the nucleus (Jenner-Giemsa × 900).

FIG. 3 (*below, center*). Reticulum cell with large nucleus containing several large nucleoli (Jenner-Giemsa × 900).

FIG. 4 (*below, right*). Possible intermediate cell type beneath a Gaucher cell. Note the relatively small nucleus and abundant cytoplasm of the intermediate cell as compared to the reticulum cell in figure 3 (Jenner-Giemsa × 900).

exist between the coarse purple chromatin aggregates. A small blue nucleolus is frequently present. The pale blue cytoplasm contains many fine particles and linearly arranged fibrils several micra in length, groups of which course in varied directions. Portions of the cytoplasm often appear to be unstained, the amount varying greatly in individual cells. The cell boundaries tend to be indistinct, particularly when the characteristic cells are in contact with each other. Occasionally, one or several erythrocytes, leukocytes or platelets appear to be present within the cytoplasm of the Gaucher cells (figure 2).

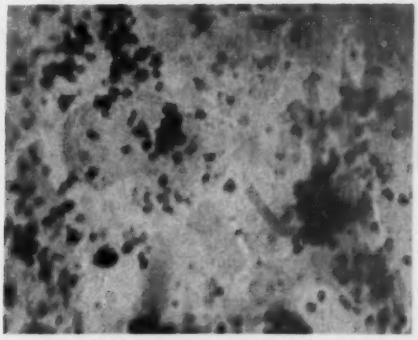

FIG. 5. Chronic hemolytic anemia with transfusion siderosis. The numerous intensely staining iron-positive particles appear to be predominantly extracellular in location (Prussian blue, safranine × 900).

In addition to the characteristic cell, the bone marrow in this disorder often contains many smaller, mononuclear cells. They appear to be reticulum cells, which normally are present only in small numbers in the marrow.[15] Though roughly proportionate to the quantity of the large cells present, they constitute less than 5% of the non-Gaucher nucleated cell count. The nucleus of this type of cell is more nearly reddish purple in color, and its chromatin is less coarse than that in the Gaucher cell. In addition to being both absolutely and relatively larger in size, occupying at least one-half of the 20- to 30-micra diameter of the cell, the nucleus differs from that of the Gaucher cell in having several large, light blue nucleoli (figure 3). The cytoplasm is usually a darker shade of blue and more homogeneous. Both the nucleus and the cytoplasm frequently have many minute, round, unstained areas, about 1 μ. in diameter, which may be artifacts.[16] The cell margins often tend to be indistinct, but less so than in many Gaucher cells, and there is a lack of cytoplasmic fibrils. Certain cells appear to have some characteristics of both the reticulum and Gaucher cells, suggesting that they might be intermediate forms in the development of the latter (figure 4).

As smears rather than sections of the bone marrow were studied, thus disturbing the architecture, it is not possible to comment on the appearance of the endothelial cells of the marrow sinusoids.

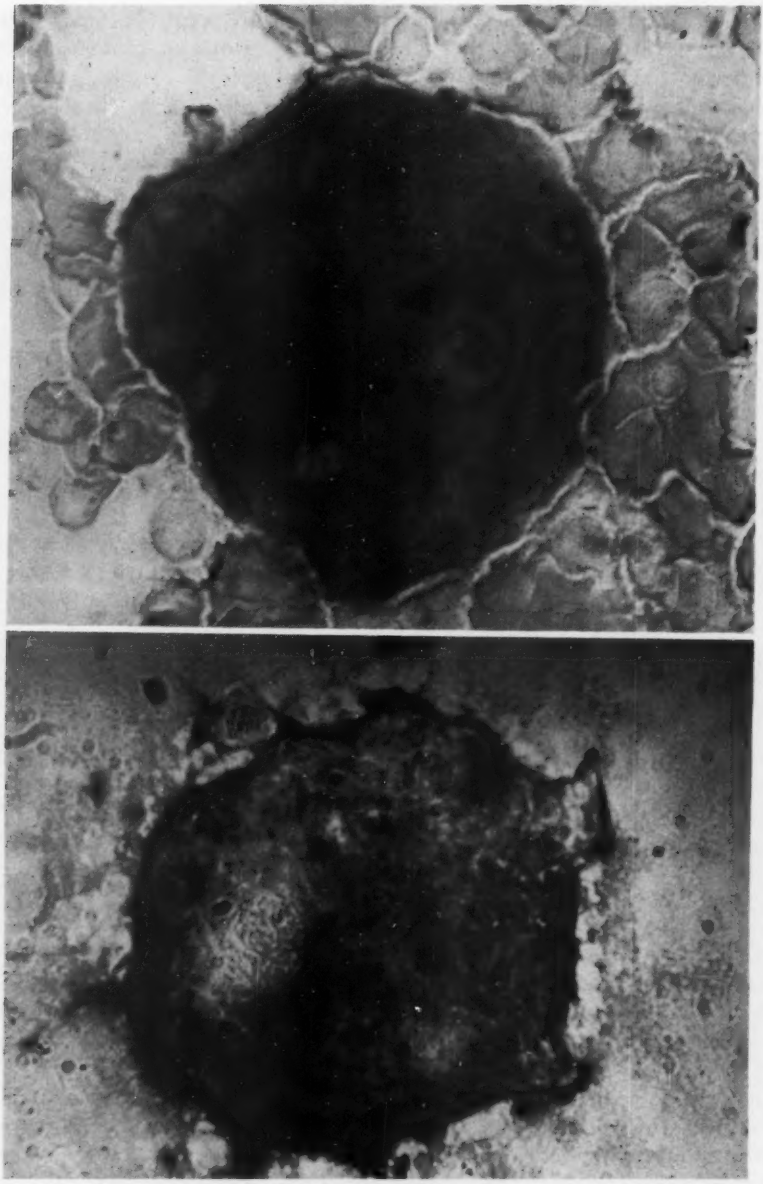

FIG. 6 (*above*). Gaucher cell. Note the diffuse, but not homogeneous, staining of the cytoplasm, indicating the presence of iron, the lack of staining of the nuclear areas, and the lack of tiny extracellular iron-containing particles such as those seen in figure 5 (Prussian blue, safranine × 1200).

FIG. 7 (*below*). Gaucher cell. The prominent staining of the cytoplasm is in contrast to the nuclear areas. At the upper border of the cell a normoblast appears to be engulfed in the cytoplasm (Prussian blue, safranine × 1200).

In all the Gaucher cases, Prussian blue-stained marrow smears had many iron-containing structures which were easily visible under low power magnification. They were of much larger size, although far less numerous, than those present in hemosiderosis. Whereas in the latter condition the iron deposits are particulate, being about several micra in diameter (figure 5), in Gaucher's disease the characteristic large cells themselves give the reaction for iron (figures 6 and 7). Their blue cytoplasm ranges from a pale to a very dark hue, and is not homogeneous; numerous pale streaks or zones are often present between denser areas. The tiny fibrils seen in Jenner-Giemsa-stained cells are not clearly seen with the Prussian blue technic. The nuclei are stained only by the counterstain, indicating an absence of stainable iron.

By contrast, the reticulum cells do not stain with Prussian blue, as has been noted by others.[17] It cannot be said whether there is iron in the postulated intermediate forms, as cellular detail is not too apparent with this technic, so that such cells either do not stain or, if they do, their resemblance to small Gaucher cells is too great to permit definite differentiation. Ordinary fat cells are not stained by Prussian blue.

Normal bone marrows, and particularly bone marrow from the case of chronic hemolytic anemia and transfusion siderosis, besides containing 1 to 2 micra iron-positive extracellular particles, also have occasional small, iron-containing cells, presumably histiocytes. They are not nearly so large or so numerous as the characteristic cells which occur in Gaucher's disease, but are also part of the reticuloendothelial system. In all cases, reticulum cells, megakaryocytes and myeloid cells do not stain with Prussian blue.

To investigate the possibility that the iron might be associated with the kerasin, the Prussian blue technic was performed on purified normal kerasin obtained from the Bios Laboratories of New York and prepared by them according to the technic of Thierfelder and Klenk.[18] Negative results were obtained, suggesting that iron is not intimately associated with kerasin, or at least may be separated from it.

Discussion

1. *Iron Stains:* A number of technics have been described for demonstrating the presence of iron in tissues.[13, 19] Some stain primarily the ferrous form (Quincke's ammonium sulfide, Turnbull's blue), and others, the ferric form (Prussian blue). However, many iron-containing substances, such as hemoglobin, are not demonstrable by these methods.[19, 20] In the case of the Prussian blue reaction, the numerous modifications of the basic procedure which exist[14, 19, 21-28] hamper attempts at exact comparison of various reports. In addition, despite Bunting's contention to the contrary,[26] there is doubt that ferrous compounds occur naturally.[19, 29] If this be true, negative reports of iron in tissues stained with Turnbull's blue are of doubtful value. All of these factors make much of the published information concerning tissue iron localization difficult to evaluate.

2. *What Is Stained by an Iron Stain?* Stainable tissue iron occurs in two related forms, ferritin and hemosiderin, both having the same iron micelles.[30] Both are also considered to have similar functions in the storage of iron,[31, 33] but the former may be more active in iron equilibrium because of its smaller size. Ferritin consists of about 25% apoferritin molecules free from iron, the remaining 75% having iron firmly bound to protein.[34] It occurs in minute crystals having a relatively large surface area, in contrast to hemosiderin, which is composed of dense,[30] abnormally large and cross-linked ferritin molecules,[35] forming granules.[32] The bluish color of cytoplasm in Prussian blue-stained material has been ascribed to ferritin.[36] Granick,[35] however, states that ferritin is ordinarily too diffuse to be microscopically visible; the prominent staining of Gaucher cells may therefore signify the presence of an unusually large amount in those cells.[10, 30] Some workers [6, 28, 37] call iron "hemosiderin" whether present in a granular or a diffuse form. Perhaps that term should be reserved for definite granules, brownish yellow when unstained, and occurring both within and outside cells; and ferritin should be applied to the more diffuse intracellular form of tissue iron.

3. *Tissue Iron in Gaucher's Disease:* The first paper to mention the presence of iron in this disorder was by Brill et al.[3] They noted extracellular iron pigment in the pulp spaces, trabeculae and capsule of the spleen, and in the sinuses and trabeculae of lymph nodes. Nine years later, Brill and Mandelbaum [38] noted brownish yellow granules within the characteristic cells. The first observations of intense, diffuse staining of the Gaucher cells with a Prussian blue technic were made shortly thereafter,[39, 5] and were subsequently reaffirmed.[37, 40] However, it has also been stated [5, 6, 17] that, in the absence of large hemorrhagic areas, the intracellular iron pigment either occurs in minute quantities or is entirely absent.

With Turnbull's blue, Bloom, as well as Pick,[6] noted a diffuse pale blue color in the characteristic cells of Gaucher's disease, in contrast to those of Niemann-Pick disease.[41] Others,[42] though also using Turnbull's blue, did not note staining of the former cells. Likewise, with Prussian blue, Morgans [44] and Block and Jacobson [17] reported cases of the so-called "osseous" type,[43] where the spleen is not palpable, and where characteristic cells had a negative staining reaction for iron. However, one of the present cases also had no splenomegaly, yet had marked accumulation of iron in her Gaucher cells.

4. *Relationship of Tissue Iron to Hemolysis:* Older reports concerning tissue iron in Gaucher's disease emphasized extracellular hemosiderin deposition in the liver and spleen,[3] particularly in long-standing cases with hemorrhagic areas [5, 38] in various organs. It has frequently been stated that the iron pigment within Gaucher cells originates from the phagocytosis of erythrocytes or hemoglobin products [5, 6, 38, 39] and that increased hemolysis is a common [45] if not a constant [6] occurrence. Wintrobe,[15] on the

other hand, states that there is no increased blood destruction in this disorder, essentially supporting the contention of others.[47, 48]

Fienberg and Quigley [37] observed erythrophagocytosis and iron within Gaucher cells in a subject who had 13 gm.% hemoglobin and 0.9% reticulocytes, surely not suggesting that hemolysis was very active. Nevertheless, they stated that iron deposition occurs only in the presence of moderately severe hemolysis. However, Popper [46] says that fragmented red cells may be found in the Kupffer cells of normal individuals, thus indicating that a certain amount of erythrophagocytosis by cells of the reticuloendothelial system should not necessarily be considered pathologic, although admittedly it is not ordinarily seen in the normal bone marrow. Others,[47] using elevation of the indirect reacting serum bilirubin or reticulocytosis as criteria, noted but slight evidence of increased hemolysis in 29 cases of Gaucher's disease. More recently, in two cases, Decker and McWhorter [48] were not able to demonstrate hemolysis either by determination of fecal urobilinogen or by the Coombs' test. However, cortisone was beneficial, suggesting to the authors that hypersplenism was present. In addition, the skin pigment in several cases of this disorder [42, 49] has been shown to be, not iron, but melanin. These studies thus do not support the contention that appreciable hemolysis with secondary hemosiderosis is a constant occurrence in Gaucher's disease. Likewise, even though minimal erythrophagocytosis was present in all, three of the five cases mentioned in this paper had no anemia or reticulocytosis, and four had never received transfusions, minimizing the likelihood of a significant hemolytic process being responsible for the large amount of iron demonstrated in their Gaucher cells. Furthermore, comparison of Prussian blue-stained bone marrow smears in the Gaucher cases with the bone marrow smear from the case of chronic hemolytic anemia with transfusion hemosiderosis revealed that the latter had very many minute, iron-positive particles, presumably originating from destruction of the patient's own as well as transfused erythrocytes. These were infinitely more numerous than in the Gaucher cases, in whom the amount of such particles was normal, again suggesting that the Gaucher cases' tissue iron did not originate from predominantly extravascular erythrocyte breakdown, or at least that its magnitude was not comparable. If, as may be possible, the particles observed in the patients with hemosiderosis originated from the disruption of histiocytes while making the smears, then perhaps the latter may be more numerous or more fragile in that condition than in Gaucher's disease.

5. *Origin of Gaucher's Cells:* The belief that Gaucher's disease is a condition involving the reticuloendothelial system was first postulated by Schlagenhaufer,[4] and shortly thereafter adhered to by others.[5, 6] It has been reported [46] that the transformation of Kupffer and other mesenchymal cells to Gaucher cells may actually be seen in histologic sections. The venous sinus endothelium was excluded by some as a source of the characteristic

large cells, due to its considerable iron content,[6, 17] in contrast to the alleged lack of iron in the Gaucher cells. Unfortunately, observations on sinus endothelium are not possible to make on smears, but only on sections; thus this paper cannot comment on that hypothesis except insofar as current observations indicate that iron does exist in Gaucher cells. Other possible precursors reported have been fibroblasts, osteoblasts, osteoclasts,[17] and perivascular connective tissue cells.[7] The present findings—that the number of cells resembling the usual reticulum cells in the bone marrow is roughly proportionate to the number of Gaucher cells, plus some general similarity of structure [16] and the presence of presumed intermediate forms—lead the author to agree with others [4-6, 16, 50] that the two types of cells are related, despite the differences of their iron content herein described.

6. *Possible Metabolic Abnormalities in Gaucher's Disease:* It is not the purpose of this paper to discuss the cerebroside abnormality of this condition. Suffice it to say that there is an increased amount of intracellular cerebroside,[1, 2] containing either galactose or glucose,[51] or both, not accompanied by an excess in the serum.[52, 53] Thannhauser [54] postulated an imbalance of enzymes concerned with lipid metabolism, and Uzman [55] has mentioned the possibility of a defect in the protein-synthesizing matrix of the reticuloendothelial cell resulting in a protein's having an abnormal affinity for kerasin and being resistant to enzymatic hydrolysis in vitro, and perhaps in vivo.

The relationship of kerasin to intracellular iron is unknown, but the lipoprotein does not give a Prussian blue reaction, indicating that, although both are prominent components of the cytoplasm they are not inseparably linked. The presence of iron in Gaucher cells is another example of the association of iron with abnormal lipid-containing tissues, as has also been noted in xanthomata.[19, 24] It has been stated [56] that iron pigment can occur in hepatic cells when the nutrition of the tissues is impaired. Perhaps similarly in Gaucher's disease, the accumulation of lipid may alter cellular function, disturbing the normal iron metabolism in some unexplained manner. The converse may, however, apply,—i.e., Granick [35] believes that if the "proper kind" of ferric hydroxide is not present, its absence may cause cell destruction by precipitating proteins or by inactivating one or more specific intracellular enzymes. If that is correct, then this apparent lipoid disorder might conceivably be dependent upon an abnormality of iron metabolism. However, at the present stage of knowledge this is sheer speculation. It may merely be that iron is in Gaucher cells because they are components of the reticuloendothelial system, as are the Kupffer cells of the liver and the histiocytes of the spleen. However, Thannhauser [54] states that, although granular hemosiderin may be present in the trabeculae, sinus walls and Gaucher cells of the spleen, the Kupffer cells of the liver usually appeared to be normal despite their phagocytic function.[46] In addition, many or most Niemann-Pick cells,[41] and perhaps related cells,[57] may develop from reticulo-

endothelial cells, yet do not appear to contain iron, so that it is not always evident that all cells derived from the reticuloendothelial system contain iron.

That Gaucher's disease is not purely a disorder characterized by the accumulation of abnormal lipids has been shown by Sobotka et al.,[58] who demonstrated a deficiency of liver esterase, and by Tuchman et al.,[59] who demonstrated an elevation of serum acid phosphatase. Therefore, should a possible metabolic abnormality [60] be responsible for the striking accumulation of iron within the characteristic cell, it would be another in the ever-widening spectrum of biochemical dysfunction associated with Gaucher's disease.

Summary

The marked amount of intracellular iron observed within the characteristic cells in five cases of Gaucher's disease does not seem compatible with the minimal erythrophagocytosis present in all of the cases, or with the absence of anemia and reticulocytosis in three of them, thus minimizing the possible role of abnormal hemolysis in causing the tissue iron deposition. Nevertheless, it may very well be that part of the iron does derive from the ingestion of red cells by Gaucher cells.

A purified specimen of normal kerasin contained no iron that was demonstrable by the Prussian blue procedure, suggesting that neither does the iron-staining occur as a necessary manifestation of the presence of kerasin within the large cells.

The diffuse iron-staining of the characteristic cells resembles that noted in many cells of the reticuloendothelial system, such as histiocytes in the spleen and Kupffer cells of the liver, and may merely indicate a relationship to that system. However, in the reticulum cells of the bone marrow, from which many Gaucher cells presumably arise, as well as in some pathologic cells derived from that system, no such staining occurs. The possibility therefore exists that the unusual accumulation, presumably of ferritin, within the cytoplasm of developing Gaucher cells may be evidence for the presence in this disease of an as yet unidentified metabolic abnormality involving iron, in addition to the known alterations of such substances as kerasin, liver esterase and serum acid phosphatase.

Addendum

Dr. Abraham Mazur, of the Department of Medicine, New York Hospital-Cornell Medical Center, kindly supplied a hemosiderin-free solution containing recrystallized horse spleen ferritin having 14.2 mg. total iron and 7.6 mg. total nitrogen per milliliter.[61] Two one-hundredths of a milliliter of this solution when tested for 10 minutes with Prussian blue (three parts 1% hydrochloric acid and one part 2% potassium ferrocyanide) gave a definite positive reaction, even at a titer of 1 : 1000. This supports the contention expressed herein that the iron-containing compound within the Gaucher cell, which is easily stainable by the above technic, may possibly be ferritin, despite reports minimizing the stainability of this substance by the usual methods for demonstrating tissue iron.

SUMMARIO IN INTERLINGUA

Le studio histologic del cellulas characteristic obtenite per aspiration de medulla ossee in cinque casos de morbo de Gaucher demonstrava in omnes un positive reaction tinctural a blau de Prussia, indicante le presentia de ferro intracellular. Tincturation de Jenner-Giemsa demonstrava non solmente le grande celluluas que es typic del condition, con un o plure nucleos basophilic e cytoplasma fibrillar, sed etiam certe plus micre cellulas mononuclear, cata un con un disproportionalmente grande nucleo de color rubiastre violette que contineva plure pallide nucleolos blau e un plus homogenee cytoplasma basophilic que le cellulas de Gaucher. Es opinate que iste plus micre cellulas representa stadios intermediari in le disveloppamento del cellulas de Gaucher ab cellulas de reticulo. Nulle ferro esseva demonstrate in le cellulas de reticulo.

Le distribution del ferro intra le cytoplasma del numerose cellulas de Gaucher es de character diffuse. Isto contrasta marcatemente con le constatationes in un caso de chronic anemia hemolytic con siderosis de transfusion in que depositos de ferro particulate esseva presente intra le minus abundante histiocytos, insimul con numerose tal particulas de sito extracellular.

Negative resultatos esseva obtenite con le tincturation a blau de Prussia quando illo esseva applicate a purificate kerasina normal, indicante que ferro non es intimemente ligate a lipido o, al minus, que illo pote esser separate ab le lipido e que, per consequente, le presentia de illo es possibilemente non un manifestation inherente del presentia de kerasina intra le cellulas de Gaucher sed plus tosto un disordine separate.

Es presentate le suggestion que le forma diffuse de ferro intracellular—del typo abundante in cellulas de Gaucher e que non es visibile usque illo es tincturate—es ferritina e que le forma granular—que occurre in altere conditiones tanto intra como etiam extracellularmente e que es frequentemente apparente mesmo sin tincturation specific—es hemosiderina.

In le passato, plure investigatores ha attribuite le presentia de ferro tissutal in morbo de Gaucher al occurrentia de areas hemorrhagic o a un active processo hemolytic. Tamen, tres del cinque patientes in le presente studio habeva nivellos normal de hemoglobina, sin reticulocytosis, e omnes—excepte un qui habeva un concomitante acute leucemia myelogene—habeva nunquam recipite un transfusion de sanguine. Assi, le probabilitate de significative grados de hemolysis esseva absente in le majoritate del casos, sed omnes revelava le presentia de abundante ferro intracellular, con un morphologia e un distribution differente ab illos trovate in le cognoscite caso de chronic anemia hemolytic con siderosis. Tamen, in omne le cinque casos del presente studio, grados minimal de erythrophagocytosis per alicun cellulas de Gaucher esseva notate in frottis de medulla ossee. Iste processo esseva possibilemente responsabile pro un parte del observate ferro intracellular.

Es opinate que cellulas de Gaucher se disveloppa ab cellulas de reticulo e que, in le curso de iste transformation, le cellulas de reticulo accumula non solmente le characteristic cerebrosido kerasina sed etiam abundante quantitates de ferro. Il es non ancora cognoscite si le duo substantias appare simultaneemente in le curso del disveloppamente del grande cellulas o si le un representa un condition predisponitori pro le accumulation del altere. Iste association de ferro con tissu a contento lipidic non es unic. Illo etiam occurre in xanthomas e in cellulas hepatic quando le alimentation del tissu es vitiate. Tamen, non omne cellulas que es considerate como derivate ab cellulas de reticulo se distingue, secundo le reportos, per un contento de ferro (i.e., cellulas de Niemann-Pick).

Morbo de Gaucher deberea non plus esser considerate como le manifestation de un isolate defecto de cerebrosido, proque il ha in plus in iste condition un elevation del nivello seral de phosphatase acide e un deficientia de esterase hepatic. Il etiam

existe le possibilitate que un anormalitate metabolic es responsabile pro le frappante accumulation de ferro intra le cellulas characteristic de morbo de Gaucher. Assi il pare que un dysfunction biochimic additional ha essite demonstrate como associate con iste disordine inusual.

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A PRACTICAL, SYSTEMATIC LABORATORY APPROACH TO THE STUDY OF THE PERIPHERAL CIRCULATION * †

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DURING the last decade rapid strides have been made in the medical and surgical therapy of peripheral vascular disease. It has therefore become increasingly important to obtain accurate and objective information concerning the state of the peripheral circulation before and after various types of therapy. Ideally, this information should be objective, complete, permanent, accurate, and obtainable at desired intervals without mortality or morbidity secondary to the technics employed.

The purpose of this review is to describe a practical laboratory approach to the study of peripheral vascular functions as an aid in the diagnosis and treatment of the peripheral vascular diseases.

METHODS

The instrument (Vasograph ‡) used for most of the studies was a console model containing three electronic segmental limb pneumoplethysmographs,[1] three electronic digital pneumoplethysmographs,[2] a pressure panel and three temperature measuring thermistor thermometers.[3]

Segmental limb plethysmographs were used to measure the limb pulsations at various locations on the arms and legs; the tracings were recorded in cubic centimeters of volume change per beat. Digital plethysmographs were used to measure the systolic blood pressure at various levels on the limbs and to record the pulse waves (in cubic millimeters) and blood flow (in cubic millimeters per second) in the digits, the latter making possible a study of the circulation through the small terminal vessels. These plethysmographs are equipped with standardizing devices so that the volume change may be recorded and compared with records made at different times or in different laboratories. The thermistor thermometers were applied to the second toe of each lower extremity and the second finger of either upper

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extremity with elastic cellulose tape, and simultaneous records were obtained during the course of the study.

Routine Measurements: These consisted of blood flows, pulse volumes and skin temperatures of the digits, pulsations and systolic blood pressures from various locations on the arms and legs (above the elbow, wrist, groin, above the knee, below the knee and ankle). Vasodilatation was produced and the digital measurements were repeated.[4, 5] Appropriate corrections were made for curvilinear paper.

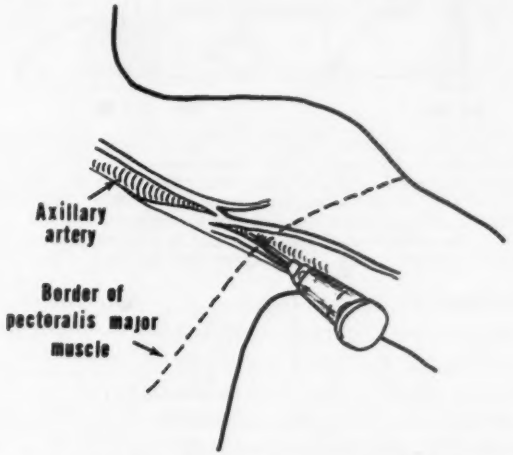


FIG. 1. The brachial plexus nerve block is accomplished by injecting a local anesthetic in the region of the axillary artery at the inferior margin of the pectoralis major muscle. The median, musculocutaneous ulnar and radial nerves are anesthetized in this area.

The vasodilating procedures were (1) a posterior tibial nerve block, (2) body heating and alcohol in a dose of 2 ounces of whiskey, (3) a brachial plexus nerve block (figure 1),[6, 7] or (4) reactive hyperemia produced by release of the circulation after from five to 15 minutes of arterial occlusion.

RESULTS

Arterial Disease

Lower Extremities: The presence of arterial disease is, as a rule, easily detectable by observing the amplitude and morphology of the pulse waves (figure 2).[8, 9, 10] The abnormal waves usually exhibit a significant decrease in pulse amplitude, an insignificant or absent dicrotic notch, a prolonged crest time, a rounded or flattened peak, and a slow rate of rise of the anacrotic limb. The site of an arterial obstructive process may be determined by studying the pulse waves. If there is an obstruction in the superficial femoral artery, the pulse waves above the obstruction will be essentially

normal in contour and of greater amplitude than normal, whereas the pulse waves below the obstruction will be reduced in amplitude, and morphologic changes will be present (figure 3A and 3B).

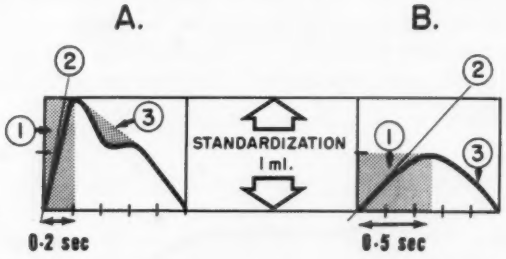


FIG. 2. The amplitude (volume change) and morphologic characteristics of the pulse curves may be employed to differentiate the normal curve (A) from the abnormal curve (B). In the normal individual (A) the pulse amplitude is 1.0 ml., the crest time (1) is 0.2 second, the rate of rise (2) is 6.0 ml. per second, the dicrotic notch (3) is present, and the peak of the wave is sharp and not rounded. In the abnormal patient (B) the amplitude is reduced to 0.5 ml., the crest time (1) is prolonged to 0.5 second, the rate of rise (2) is 1.3 ml. per second, the dicrotic notch (3) is absent, and the peak of the wave is rounded.

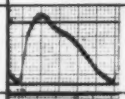
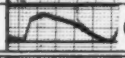
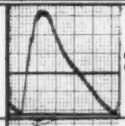
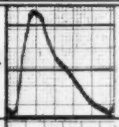
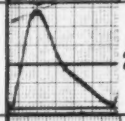
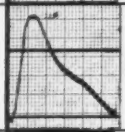
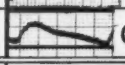
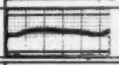
Amplitude ratios of pulsations obtained at various locations on the upper and lower extremities in 30 normal subjects have been calculated (table 1). The pulse amplitude at the groin should be at least 118% of the pulse amplitude above the elbow; if the value is less than this, an arterial obstruction probably exists at or above the groin cuff. If the groin pulsations are reduced symmetrically, the obstruction usually is located at the aortic bifurcation. By this technic, obstructions in the lower extremities between various cuff positions can be localized and estimates of the severity of the obstructive process can be made.

TABLE 1
Amplitude Ratios (in %) Calculated for Pulsations Obtained at Different Locations

Location	Min.	Max.	Ave.	Standard Dev.
Groin/Above elbow × 100	118	515	262.4	96.5
Above knee/Groin × 100	51	117	88.2	16.3
Below knee/Above knee × 100	57	127	94.8	16.9
Ankle/Below knee × 100	30	106	44.8	14.7
Ankle/Above elbow × 100	46	138	86.8	21.5

The differentiation of functional from organic occlusive arterial disease is made with the aid of a vasodilating procedure such as a posterior tibial nerve block. If organic arterial occlusive disease is present the blood flow and pulsations to the toe are low before the block and remain low after the block. If a strong functional vasoconstriction is present the posterior tibial nerve block will eliminate or decrease vasoconstrictor tone, which will allow the blood flow and pulsations to the toe to increase greatly after the block (figure 4).

B.

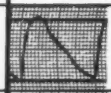
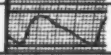
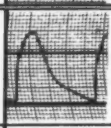
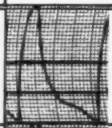
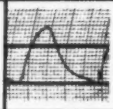
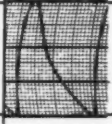
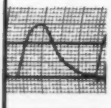
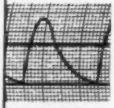
PULSATIONS							
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Above elbow	 1.1		.7 .4-1.2	130		134 80-148
Wrist	 0.6		.4 .2-.5	110		128 80-130
Groin	 2.4	 2.3	1.8 1.2-2.9	150	150	147 132-228
Above knee	 2.0	0.6	1.5 .9-2.0	140	50	140 130-220
Below knee	 1.5	0.4	1.3 .9-1.9	130	36	130 110-164
Ankle	 0.6	 0.2	.5 .3-.7	105	30	120 80-138
Ab. knee / Ab. elbow	1.81	0.54	2.1 .9-3.9	1.07	0.39	1.2 1-1.5
Ankle / Wrist	1.00	0.33	1.6 .9-2.1	0.96	0.27	1.1 .8-1.3

DIGITS									
	PULSATIONS			FLOW			TEMPERATURE		
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Fingers Before	5		6 4-8	18		15 12-32	34.0		34.0 32-36
After heat alcohol	7		9 6-12	38		45 32-64	35.5		35.5 35-36
Toes Before	2	1	3 2-7	4	1	8 4-13	27.2	26.8	31.0 28-34
After heat alcohol block	5	1	7 4-11	18	4	20 15-28	35.0	31.0	35.5 35-36

FIG. 3. A. Obstruction of the superficial femoral artery before operation. Pulsations and blood pressure are decreased on the left side below the groin. These findings are confirmed by the pulsation ratios, digital pulsations, digital blood flow and the skin temperatures. The segmental limb pulsations are in cubic centimeters, the digital pulsations are in cubic millimeters, the blood flows are in cubic millimeters per second, and the temperatures are in degrees Centigrade.

Blood flow to the calf: Technics have been worked out for studying the total blood flow to the calf plethysmographically. This involves using a triple cuff method, as follows: The recording cuff is placed at the calf and is

EXTREMITIES Af.

	PULSATIONS			PRESSURE		
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Above elbow	 1.0		.7 .4-1.2	128		134 80-148
Wrist	 0.8		.4 .2-.5	110		128 80-130
Groin	 1.5	 3.7	1.8 1.2-2.9	150	160	147 132-228
Above knee	 1.5	 3.0	1.5 .9-2.0	145	150	140 130-220
Below knee	 1.6	 1.6	1.3 .9-1.9	140	130	130 110-164
Ankle	0.6	0.6	.5 .3-.7	110	110	120 80-138
Ab. knee / Ab. elbow	1.50	3.00	2.1 .9-3.9	1.13	1.17	1.2 1-1.5
Ankle / Wrist	0.75	0.75	1.6 .9-2.1	1.00	1.00	1.1 .8-1.3

DIGITS

	PULSATIONS			FLOW			TEMPERATURE		
	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL	RIGHT	LEFT	NORMAL
Fingers Before	5		6 4-8	15		15 12-32	35		34.0 32-36
After heat alcohol	7		9 6-12	30		45 32-64	35		35.5 35-36
Toes Before	3	3	3 2-7	4	3	8 4-13	26.5	25.5	31.0 28-34
After heat alcohol block	5	4	7 4-11	20	15	20 15-28	34.5	34.8	35.5 35-36

FIG. 3. B. The same patient after insertion of a bypass graft from the common femoral to the popliteal artery on the left side. The pulsations and blood pressures are markedly increased.

inflated to 15 mm. Hg; a second cuff is placed at the ankle and is inflated to above systolic blood pressure; a third cuff is placed above the knee and is inflated to a venous occluding pressure (i.e., 70 mm. Hg). The rate of inflow of blood to the calf is determined from the increase in volume of the calf which occurs because of venous congestion. This method has been compared with the calf flow as measured by the water-filled limb plethysmograph employed by Barcroft and Swan,[11] and the results have proved to be comparable. This technic has been used for various studies and has demonstrated, for example, that nylidrin hydrochloride (Arlidin *) may increase muscle flow up to four times the control values.

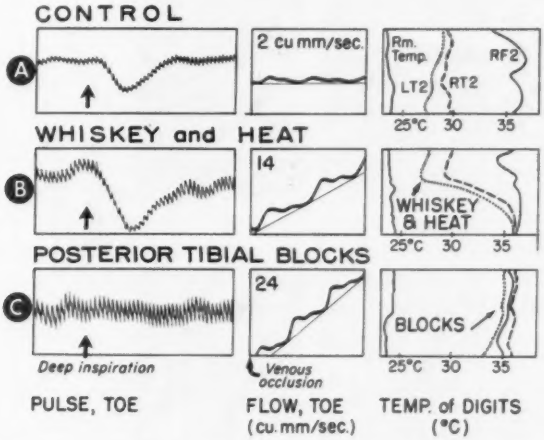


FIG. 4. Effect of vasodilating procedures on the pulse amplitude, blood flow and skin temperatures of the digits. In the control record (A) the pulse volume is low, inspiration causes a constriction, the blood flow is 2 cu. mm. per second, and the toe temperature is low. After whiskey and total body heating the pulsations increase, inspiration causes a constriction, the blood flow increases to 14 cu. mm. per second, and the skin temperatures rise. After a posterior tibial nerve block the pulsations increase further, inspiration no longer produces constriction, the blood flow goes up to 24 cu. mm. per second, but the skin temperatures remain unchanged.

Exercise tolerance tests: An exercise tolerance test may be performed, as follows: Cuffs are applied to the ankles, and the maximal pulses at the ankles are recorded by selecting the proper cuff pressure. The gain of the instrument is adjusted so that the amplitude of pulsations is 10 mm. A control record is taken with a paper speed of 2.5 mm. per second. The cuffs are deflated and the color of the feet is noted. The patient is then instructed to exercise by dorsiflexing his feet once a second until he is unable to continue exercise because of severe pain or weakness of the muscle groups. At this point the cuffs are immediately inflated to the previously determined pressures and the pulsations are recorded every 10 seconds for one minute.

* U. S. Vitamin Corporation.

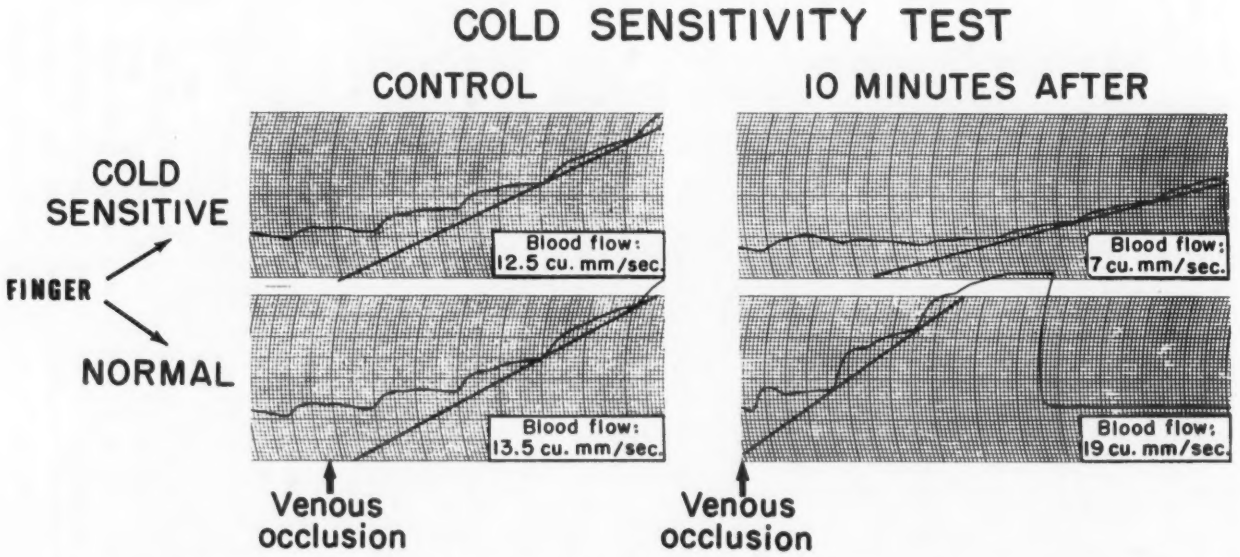


FIG. 5. Cold sensitivity demonstrated in a 45 year old male with Raynaud's phenomenon. Blood flow was measured in the abnormal (cold-sensitive) finger, and in a normal finger for a control. Measurements were made before and 10 minutes after removing hands from water 15° C. for 15 minutes. In the cold-sensitive finger the flow was less than in the control, whereas in the normal finger the flow was more than in the control after removal from the cold water.

In normal subjects, the pulse amplitude decreases slightly at 15 seconds and returns to the control value at one minute. In patients with significant arteriosclerosis obliterans there is a marked decrease in amplitude at 15 seconds, with waves of very low amplitude at one minute.[12] The test, if negative, may be repeated with the patient moving his feet against resistance. These results indicate that patients with arterial occlusive disease may, by increasing the circulation through the exercising calf, divert blood from the ankle, foot and toe to supply the exercising muscle, and thereby produce a relative ischemic state in the skin of the ankles, feet and digits, during the post-exercise period. The test is similar to that described by Ejrup.[13]

Upper Extremities: The upper extremities are a less common site for vascular disease than are the lower extremities, but the identification of disease is equally as important, and can be demonstrated by similar technics. In addition to determining the amount of functional and/or organic disease present, and locating obstructions in the arterial tree, the plethysmographic study aids in determining the presence or absence of cold sensitivity, and in ruling in or out neurovascular syndromes of the shoulder girdle.

The degree of functional vasoconstriction can be determined in the upper as in the lower extremities by noting the degree of increase in blood flow through the finger after vasodilatation with heat, alcohol, reactive hyperemia or brachial plexus block.[6, 7] Often the blood flow will increase as much as 50 times after vasodilatation in persons with functional vasoconstriction, but there will be little change in blood flow in persons who have advanced organic arterial occlusive disease.

The presence of cold sensitivity may be determined by thermal or plethysmographic examination.[3] Note is taken of the length of time required for the fingers to reach 30° C. after immersing the hands in 15° C. water for 15 minutes with the patient resting in a warm, comfortable environment. The normal individual will return to 30° C. in five or 10 minutes after the hands are removed from the cold water, whereas the patient with cold sensitivity frequently will need 90 minutes before 30° C. is reached. The test may be carried out plethysmographically by applying cups to the diseased and to a normal finger for a control (figure 5). Cold sensitivity is demonstrated in the abnormal finger which shows a blood flow lower than the normal finger 10 minutes after the hands were removed from the cold water.

Vectorplethysmography: This is a method for comparing volume changes of pulse waves from two different parts of the limbs or digits. This method makes possible an accurate analysis of differences in amplitude, time of onset, and configuration of the pulsations.[14] If one pulse is put onto the horizontal plates of the oscilloscope and the other pulse onto the vertical plates, a vector loop will result. Normally, two identical pulses would appear on the oscilloscope screen as a line running at a 45° angle to a horizontal reference line. In patients with unilateral arteriosclerosis obliterans of mild degree, this line will change its position, indicating amplitude differences in the two

waves. With moderately advanced disease an open loop is formed, indicating differences in configuration, whereas with far advanced disease, with a complete or nearly complete obstruction, time differences become apparent as the pulse velocity is slowed. The technic used is such that when arterial disease involves the limb vessels on the left the loop rotates in a clockwise direction, and when disease is present on the right the loop rotates in a counterclockwise direction. It is of particular interest that multiple lesions in a limb may be located by this method.

Venous Disease: Venous obstruction or venous insufficiency (when the arterial circulation is normal) may be revealed by applying ankle cuffs at 20 mm. Hg pressure to record the volume of the part. The legs are elevated for 15 seconds to empty the veins. The patient then sits with his legs in a dependent position. The volume increase in this position is recorded. With venous obstruction or insufficiency, swelling occurs rapidly. To help to differentiate insufficiency from obstruction, the patient dorsiflexes his feet two or three times. With insufficiency the ankle volume remains unchanged, as venous blood is not pumped out. With obstruction with sufficient valves, the volume of the ankle decreases with exercise and the volume increases rapidly when the exercise is stopped.

The Nervous System

Plethysmographic technics are effective in helping to select patients for sympathectomy, in determining the completeness of the sympathectomy immediately postoperatively, and in measuring the return of sympathetic function after surgery.

When a large increase in blood flow into the digit is produced by any of the vasodilating technics, it is probable that the increased flow is due to release of functional vasoconstriction, and a sympathectomy probably will be of value. When the vasodilating technic does not produce an increased blood flow to the digit, it is most likely that the low blood flow to the digits is due to organic arterial occlusive disease, and a sympathectomy will be of little or no value.

The evaluation of the completeness of sympathectomy and the detection of return of sympathetic function are easily performed. In patients who have had lumbar sympathectomies, posterior tibial nerve blocks are performed one month and one year after surgery. If the nerve block fails to produce an increase in flow one month after sympathectomy, the surgical procedure has interrupted sympathetic function satisfactorily.[4] An increase in flow following a block one year after surgery indicates that sympathetic function has returned, presumably by regrowth of sympathetic nerves. Also, a deep inspiration, a loud noise, or a painful stimulation of some portion of the body produces a vasoconstrictive response of the vessels of the digits if sympathetic nerves are present.

Cardiac Disease

Recording the peripheral pulse waves with the use of the plethysmograph is useful in the study of certain types of heart disease—for example, the configuration of the pulsations is distinctively altered in aortic stenosis and aortic insufficiency.[15] The similarity of the pulses recorded plethysmographically and intra-arterially has been shown.[16]

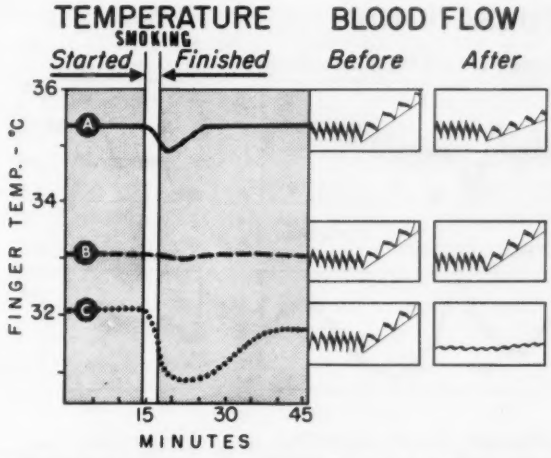


FIG. 6. Effects of smoking on finger temperature, pulse and flow. A. Normal reaction, slight decrease in all measurements. B. After cervical sympathectomy; no significant change in measurements. C. Nicotine sensitivity in a patient with thromboangiitis obliterans. All measurements are markedly reduced.

Nicotine Sensitivity

Sensitivity to tobacco may be determined plethysmographically [3] (figure 6). Vasodilatation is produced by heat and oral alcohol (if necessary), and control measurements of the blood flow and digital skin temperatures are recorded. The subject then smokes a cigarette in a period of three minutes, and measurements of the skin temperature and digital blood flow are recorded periodically for from 15 to 30 minutes. Normally, the temperature may remain unchanged, increase 0.5 to 1.0° C., or decrease not more than 2° C. for not more than 10 minutes; the digital blood flow at the end of 10 minutes usually will be normal or only slightly decreased. In the hyper-reactor to tobacco, the decrease in temperature exceeds 2° C. and the return to normal is prolonged; the digital blood flow after smoking is diminished and remains low for longer than 10 minutes. It is of interest that a sympathectomized digit fails to constrict after tobacco, as one site of nicotine action, the ganglia, has been removed. The amount of vasoconstriction is related to the nicotine and other vasoconstrictive

elements in the cigarettes, as well as to the reactivity of the vessels of the subject (figure 7).

Therapy

The plethysmograph is an effective tool in the study of the cardiovascular effects of certain drugs.[17] As an example, conditioned vasoconstrictive reflex responses were produced in individuals with the use of a soft, non-

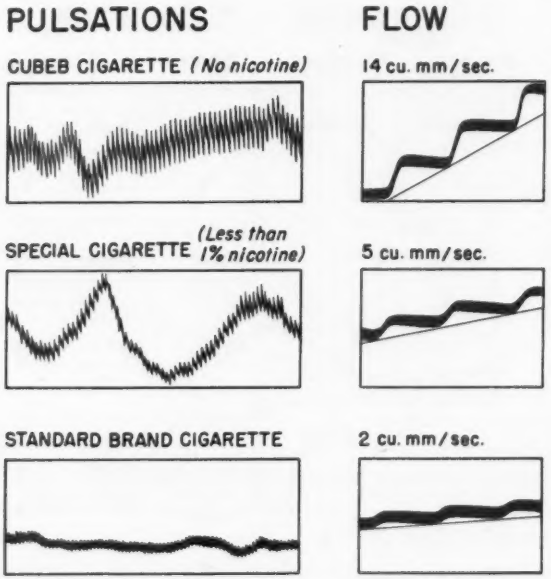


FIG. 7. Effect of different types of cigarettes on digital pulse and flow.

irritating buzzer. The conditioned response was established as follows: The buzzer was sounded and no reflex occurred. An electric shock was administered which produced a large vasoconstriction. The two stimuli were then administered together from three to 10 times. When the buzzer alone was sounded, a conditioned vasoconstrictive response occurred. Some phenothiazine derivatives interrupted the conditioned reflex without influencing the unconditioned response.

DISCUSSION

These studies indicate the multiple and varied uses of plethysmography in the study of peripheral vascular and cardiac disease. The usefulness of the plethysmograph is markedly increased because of its ability to amplify the wave forms electronically, thereby making possible a careful study of the morphology of the waves. Its accurate standardization feature makes

it possible to study the pulse amplitudes in an objective way, and the records obtained at different intervals of time or in different laboratories may be compared and evaluated.

Because the plethysmographic examination is without morbidity or mortality, one can use it repeatedly to determine the beneficial or detrimental effect of a therapeutic procedure. This laboratory study therefore becomes a valuable tool in guiding therapy, both medical and surgical.[18, 19, 20] Studies such as the exercise tolerance test, estimation of the calf muscle flow and vectorplethysmography increase our knowledge of the status of the arterial tree. The use of plethysmography in the study of the venous system is of increasing importance. Preliminary studies have demonstrated that obstruction or insufficiency of veins may be detectable plethysmographically.

Plethysmography has proved to be valuable in recording the vascular effects of certain drugs. Vasodilators, tranquilizers, ganglionic blocking agents, nicotine, etc., have had their vascular effects documented by these technics. The nicotine sensitivity test is often useful in patients with thromboangiitis obliterans who sometimes are sensitive to nicotine.

The many and varied uses of the plethysmograph are limited only by the initiative and ingenuity of the individuals using the equipment. Not only may the method be used for clinical purposes, but it is also an excellent tool for studying physiologic cardiovascular phenomena.

Summary

A practical, systematic laboratory approach to the study of the peripheral circulation is described. Electronic digital and segmental limb pneumoplethysmographs and thermistor thermometers were employed. These instruments were useful in studying (1) the lower extremities in patients with obstructive and/or functional arterial disease, (2) the upper extremities in patients with diseases such as Raynaud's syndrome, pulseless disease, cold sensitivity, etc., (3) patients before and after sympathectomy, (4) the degree of nicotine sensitivity, (5) the pharmacology of various drugs, (6) the blood flow to muscle, (7) diseases of the venous system of the upper and lower extremities, and (8) patients with certain primary cardiac diseases.

Acknowledgment

We are indebted to Miss Sally Cody for her technical assistance.

Summario in Interlingua

Es describite un practic e systematic methodo laboratorial pro le studio del circulation peripheric. Es utilisate in illo electronic pneumoplethysmographos digital e segmento-extremitatal e thermometros a thermo-resistentia. Esseva demonstrate que le utilitate del plethysmographo es marcatemente augmentate in consequentia de su standardisation e de su capacitate de amplificar le formas de unda electronicamente, de maniera que un detaliate studio del morphologia del undas deveni possibile. Registrationes obtenite in differente laboratorios o a differente momentos ab le mesme patiente pote esser comparate accuratemente. Le examine plethysmographic resulta

in nulle morbiditate o mortalitate, e illo pote esser usate repetitemente pro determinar le effecto benefic o adverse de un programma therapeutic particular. Iste instrumentos es utile in studiar (1) morbo arterial obstructive e/o functional, (2) sensibilitate a frigido, (3) sympathectomia, (4) sensibilitate a nicotina, (5) drogas, (6) fluxo de sanguine a pelle o musculo, (7) morbos del systema venose, e (8) certe disordines cardiac. Le multiple e diverse usos del plethysmographo es restringite solmente per le limites del initiativa e del ingeniositate del individuo qui usa le apparatura.

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EXPERIENCE WITH PUNCH BIOPSY OF SYNOVIUM IN THE STUDY OF JOINT DISEASE*†

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In commenting some years ago upon pathologic examination of the human joint, Hench compared this structure to an inviolate "sacred cow," and noted the infrequency of the study of joint tissue at otherwise extensive postmortem examination.[1] Despite a recent plea for regular inspection at necropsy of the readily accessible sternoclavicular articulations,[2] examination of the joints is frequently overlooked, and there has been a paucity of information concerning the appearance of the synovium in almost all except the more common forms of rheumatic disease. This deficiency was only partially offset by the use of open joint biopsy. While this means of obtaining synovium has the advantage of providing adequate tissue samples, the limitations of a technic which requires the services of surgeon and operating room are obvious. In recent years the development of a closed biopsy procedure utilizing the punch instrument described by Polley and Bickel in 1951 [3] has made it possible to obtain synovial tissue with relative ease.[4-8] The purpose of this report is to record our experience with the closed biopsy technic in 136 patients (142 specimens) with rheumatic disease, and to discuss the findings in terms of histopathologic correlations.

Method and Materials

This report is based upon examination of 142 consecutive punch biopsies of synovium taken from 136 patients seen in the Presbyterian-Woman's Hospital and the Rheumatology Clinic of the University of Pittsburgh Medical Center.

In all instances, specimens were obtained from the suprapatellar bursa of one or both knees. The operator (G.R.) wore sterile gown and gloves, and followed the procedure employed by Polley and Bickel,[3] with the modification (suggested by Dr. A. J. Bollet) that, in those patients in whom the suprapatellar bursa was not distended by synovial fluid, the sac was filled with 0.85% sodium chloride solution before insertion of the biopsy needle. This simple step proved to be most valuable in assuring accurate placement of the instrument and successful biopsy. The injection of 40 to 60 ml. of

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the saline solution clearly delineated the bursa, which was then entered just above the upper, outer border of the patella. Whenever possible, specimens were taken from at least three different sites within the bursa. Upon completion of the biopsy the knee was placed in an elastic bandage and the patient instructed to restrict motion of the extremity for 48 hours. There was only one complication of this procedure in the group: a man with multiple myeloma and bleeding tendency developed pain and swelling of the knee, which subsided following the aspiration of bloody synovial fluid from the distended joint.

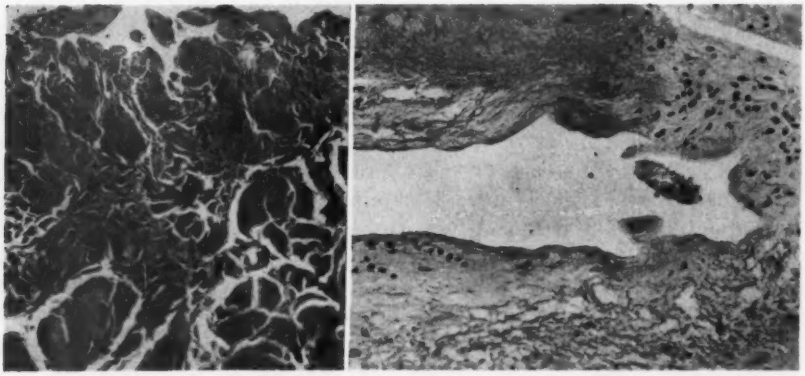

FIG. 1. *Sclerotic atrophy.* A (*left*). Small hyalinized papillary projection with scant, small synovial lining cells. Paucity of vessels. × 110. B (*right*). Homogeneous or fibrillar collagen throughout the stroma. Surface devoid of cells. × 110.

One hundred thirty-eight of the 142 biopsy specimens were considered to be adequate for histologic examination. Those attempts which failed to provide sufficient tissue were done before the instillation of sodium chloride solution into the undistended suprapatellar bursa had become a routine practice.

The histologic appearance of the biopsy specimens was compared with that of synovial tissue taken at necropsy from the open knee joints of 75 subjects clinically free of joint disease. Hematoxylin and eosin stains were employed routinely for all tissues. Masson trichrome, PAS, and azure A stains were used in selected cases. The study of material obtained at postmortem examination confirmed the observations of others [9, 10] that there are marked variations in the appearance of synovium taken from different sites within the knee joint. With these expected variations taken into account, the autopsy specimens could be separated into three general groups, designated as (a) *normal,* (b) *minimal inflammation,* and (c) *sclerotic atrophy.* Criteria for the latter two were: (b) *minimal inflammation:* varying degrees of proliferation of synovial lining cells, edema, increase in numbers of vessels, and amounts of collagen in the stroma; sparse lymphocytic infiltration,

usually in a random distribution; and (c) *sclerotic atrophy:* flattening of, and decreased numbers or complete absence of, synovial lining cells; hyalinization of the stroma, usually homogeneous or in broad bands, and hyaline thickening of capillary and arteriolar walls; inflammatory changes absent or minimal (figures 1A and 1B).

After grouping of the autopsy specimens in this manner, the cases were arranged according to the age of the patients. Although the numbers are small, there was correlation of these findings with age, in that no synovium labeled as *sclerotic atrophy* was noted in patients under 60 years, and only one labeled *minimal inflammation* was seen under the age of 40 (table 1).

TABLE 1

Histologic Changes in Knee Synovium in Relation to Age

(Autopsy Specimens)

Age Group	Normal	Minimal Inflammation	Sclerotic Atrophy
61 yrs. or older	18	10	9
41–60 yrs.	16	11	0
40 yrs. or younger	10	1	0

Histologic review of the biopsy specimens was then undertaken without knowledge of the clinical diagnoses. These were divided into a number of groups on the basis of criteria adopted from our previous experience and that of other reports.[9-11]

1. *No disease:* This included all specimens histologically resembling those observed in the categories previously described in material obtained at necropsy and believed to be unrelated to rheumatic disease.

2. *Synovitis, nonspecific:* In general, these samples were similar to the group designated in the autopsy series as *minimal inflammation,* but showed quantitatively more pronounced changes. In the majority of these, the cellular infiltrate was limited to lymphocytes. In the few in which there was fibrin and/or polymorphonuclear neutrophilic cells, the synovitis was designated as acute.

3. *Questionable rheumatoid arthritis:* The changes were similar to those described under *nonspecific synovitis,* with the addition of more focal accumulations of lymphocytes and, in some instances, small numbers of plasma cells. Occasional deposits of fibrin or fibrinoid material were seen. Edema, fibrosis and vascular proliferation were minimal.

4. *Rheumatoid arthritis:* The differences between this and the preceding group were both qualitative and quantitative. In general, the inflammatory reaction was more pronounced (figure 2). This was particularly true with reference to plasma cells which, in this group, were prominent. In addition, the inflammatory infiltrates were often distinctly focal, to the point of forming "lymphoid nodules." In some instances there were deposits of fibrin or

fibrinoid matter as well as varying degrees of edema. Vascular proliferation was present in all cases, and in some it was pronounced.

5. *Other "specific" synovitis:* The changes observed in the synovium of the patients with gout, scleroderma and neuropathic joint disease were considered to be specific, and will be discussed in more detail subsequently.

Rheumatoid Arthritis

In 37 patients, use of the criteria set forth by the American Rheumatism Association [11] justified the diagnosis of rheumatoid arthritis. The majority were hospitalized at the time of study, and in many the joint disease was widespread, severe and active. Most patients had received a variety of medications, including salicylates and anti-inflammatory steroids.

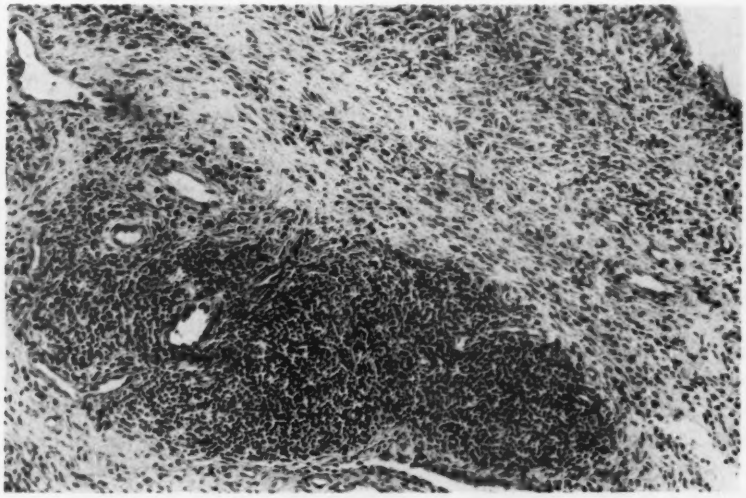

Fig. 2. *Rheumatoid arthritis.* Small amount of fibrin on surface (upper right). Numerous capillaries and mononuclear inflammatory cells, chiefly plasmacytes in stroma. Large focal collection ("lymphoid nodule"). × 110.

Punch biopsy of the suprapatellar bursa in those cases of acute joint inflammation yielded friable, dull reddish brown tissue. In a number of patients with long-standing disease which was relatively inactive at the time of biopsy, the specimens of synovial tissue were less abundant and frequently were obtained only with difficulty from what appeared to be contracted suprapatellar bursae. In one case the tissue was insufficient for histologic diagnosis.

The correlation between clinical status of the joint disease and histologic appearance of the synovium is indicated in table 2. It will be noted that in 24 of 26 patients with active involvement of the knee there were changes in

the biopsy specimens considered to be at least in the category of *questionable rheumatoid arthritis,* and in 17 the findings were sufficient to place them in the category of *rheumatoid arthritis.* None of the patients with clinically inactive disease in the knee was found to have histologic evidence of active synovitis. The category of *questionable rheumatoid arthritis* was originally designated as such because the histologic changes resembled those seen in active rheumatoid arthritis, but were not sufficiently pronounced to make this diagnosis. It was hoped that these might represent early or inactive disease, but this was not found to be the case. That these changes were encountered in a variety of conditions will be evident in the discussion of

TABLE 2

Rheumatoid Arthritis

Correlation of Clinical and Histopathologic Data

(36 cases)

Clinical Status	ND	SNS	?RA	RA
Active rheumatoid arthritis in knee, with or without evidence of activity in other joints (26 cases)	0	2	7	17
Active rheumatoid arthritis in other joints; knee joint clinically negative (4 cases)	1	1	2	0
Clinically inactive rheumatoid arthritis (6 cases)	1	3	2	0

ND = No disease.
SNS = Synovitis, nonspecific.
?RA = Questionable rheumatoid arthritis.
RA = Rheumatoid arthritis.

other diseases. An attempt to relate the histologic changes in the synovium to the duration of arthritis met with limited success. In 14 cases the duration of active joint disease was six months or less. In eight of these the presence of large amounts of fibrin or fibrinoid and polymorphonuclear neutrophilic leukocytes was considered to be indicative of the relative acuteness of the inflammatory process. These changes, described by Kulka et al.[12] in early rheumatoid arthritis, were observed as well in some patients without rheumatoid arthritis, and do not in themselves appear to be sufficient for the diagnosis of rheumatoid arthritis.

In summary, examination of the biopsy specimens disclosed pronounced histologic changes in the synovium in rheumatoid arthritis which could be correlated with the presence of clinically active joint disease. It appears that the variation in apparent acuteness of the tissue inflammation is dependent only in part upon the duration of the joint disease. The chief problem, from the standpoint of tissue diagnosis, as has been emphasized by Sherman,[13] is that these changes are not *specific* for rheumatoid arthritis. This matter will be discussed in more detail under the following sections.

Systemic Lupus Erythematosus

In 11 patients, characteristic clinical findings and the finding of a positive L.E. cell reaction were considered to be sufficient to establish the diagnosis of systemic lupus erythematosus. There were three other individuals thought to have this disorder whose serum failed to evoke the L.E. cell reaction; these patients have been included as cases of suspected systemic lupus erythematosus.

All 14 of these patients presented a history of current or remote involvement of the joints. In 10 cases the symptoms had been present for less than three years, in the form of either joint pain or frank polyarthritis. There was evidence of active arthritis in eight at the time of synovial biopsy.

In three instances the biopsy specimens were insufficient for study, leaving 11 cases for clinicopathologic correlation (table 3). No histologic

Table 3

Systemic Lupus Erythematosus

Correlation of Clinical and Histopathologic Data

(11 cases)

Clinical Status	ND	SNS	?RA	RA
Arthritis active L.E. preparation positive (5 cases)	0	3	0	2
Arthritis inactive L.E. preparation positive (3 cases)	0	1	2	0
Arthritis active L.E. preparation negative (3 cases)	1	1	0	1

ND = No disease.
SNS = Synovitis, nonspecific.
?RA = Questionable rheumatoid arthritis.
RA = Rheumatoid arthritis.

changes were encountered which were considered to be specific for the synovium in systemic lupus erythematosus. Neither fibrin nor fibrinoid was seen with greater frequency than in rheumatoid arthritis, nor was the consistent absence of inflammatory cells described by Bennett and Dallenbach [14] found in these cases. We agree with those [7, 8, 15] who believe that the synovial changes in systemic lupus erythematosus either are nonspecific, or resemble those seen in rheumatoid arthritis.

Progressive Systemic Sclerosis

In seven patients the diagnosis of progressive systemic sclerosis was established on the basis of clinical findings and histologic examination of the skin. These subjects all had pain and stiffness of the fingers and one or more peripheral joints, most commonly the wrists and knees. Of this group, one was found to have histologically normal synovium, one slight atrophy not differing significantly from that seen in normals, while five were discovered to have a distinctive abnormality [16] (figures 3A and 3B).

These showed marked atrophy of synovial lining cells, hyalinization of the stroma, and a striking decrease or almost complete absence of stromal capillaries. There was condensation of the stroma at the surface in the form of a distinct band of dense eosinophilic material. This was found to be patchy in the larger specimens subsequently studied in autopsy material. In three instances there were focal deposits of fibrin on the surface and fibrinoid material immediately beneath the surface. In only one case was

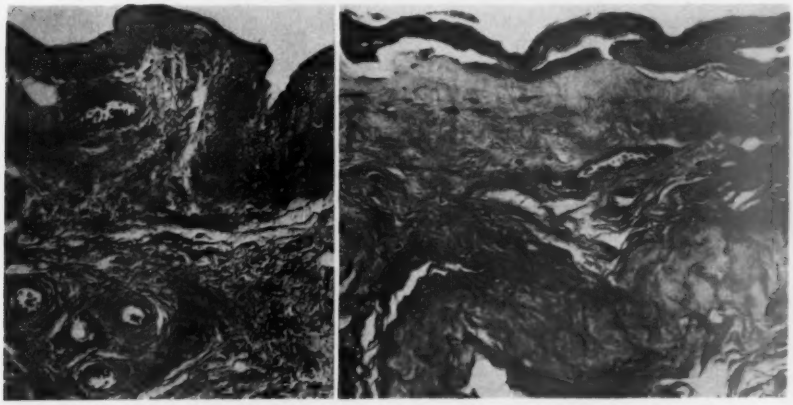

FIG. 3. *Progressive systemic sclerosis.* A (*left*). Absence of lining cells. Broad band of dense collagen near the surface. Adventitial thickening of vessels. × 110. B (*right*). More severe degree, with fibrinoid material on surface. × 110.

there any significant inflammatory reaction, this consisting of a few focal collections of lymphocytes and polymorphonuclear leukocytes. The hyalinization in the deep stroma was without special pattern, and the vessels here were inconspicuous. In one case where vessels remained there was marked concentric hyaline thickening of the capillaries. Study of autopsy material showed conspicuous adventitial fibrous thickening of larger arterioles in the stroma. Vessels of this order were not seen in the small biopsy specimens. The hyaline condensation of the stroma and focal fibrinoid deposits immediately beneath the surface have not been encountered in the material from nonrheumatic subjects labeled as atrophy or in other disease states, and are considered to be changes highly suggestive, if not pathognomonic, of progressive systemic sclerosis.

GOUT

There were 18 patients in this series in whom the diagnosis of gout appeared to be well substantiated on the basis of the clinical findings *

* These included such characteristic features as familial incidence of the disease, passage of urate stones, recurrent mono-arthritis affecting chiefly the pedal articulations, presence of subcutaneous or osseous tophi, and favorable response of acute joint inflammation to colchicine.

(table 4). Among a total of 21 synovial biopsy specimens taken from this group, there were eight (from seven individuals) which contained tophaceous matter. In seven instances, chalky bits of urate were visible on macroscopic examination of the specimen. Because of the focal nature of the tophaceous material, multiple specimens were found to be particularly helpful in this condition. In only one instance was a patient with extra-articular tophi found to be lacking in urate-laden joints. Conversely on but two occasions was tophaceous synovitis unaccompanied by any detectable subcutaneous or osseous urate deposits.

TABLE 4

Gouty Arthritis

Correlation of Clinical and Histopathologic Data

(27 cases)

Clinical Status	ND	SNS	?RA	RA	Gout
Established gout Arthritis active in knee (8 cases)	0	3	2	0	3
Established gout Arthritis inactive in knee (10 cases)	3	2	1	0	4
Suspected gout Arthritis active in knee (3 cases)	1	1	0	0	1
Suspected gout Arthritis inactive in knee (6 cases)	3	2	0	0	1

ND = No disease.
SNS = Synovitis, nonspecific.
?RA = Questionable rheumatoid arthritis.
RA = Rheumatoid arthritis.
Gout = Tophaceous synovitis.

In eight instances in this group the knee was acutely inflamed at the time of biopsy. Urate deposits were found in the synovium of two patients, both of whom had had repeated attacks of arthritis over a number of years. There were, in all, 14 patients in whom the disease had been present for five years or more; in only six was the synovial biopsy specimen found to contain urate deposits. This lack of histologically discernible tophaceous matter in the synovium of the remaining members of this group and in the majority of patients with acute gouty geniculitis at the time of biopsy suggests that urate deposits per se play little if any role in the development of acute gout.[17]

In nine patients the clinical evidence indicative of gout was deemed to be suggestive but not unequivocal prior to synovial biopsy. Of these individuals, all of whom lacked extra-articular tophi, only two were found to have synovial urate collections.*

The urates in the biopsy specimens offered no problem except that, in a few instances, multiple sections were required before they were found. The

* One of these patients has been reported in detail.[18]

FIG. 4. *Gout.* Numerous typical urate deposits. Conspicuous capillaries and mononuclear inflammatory reaction. ×110.

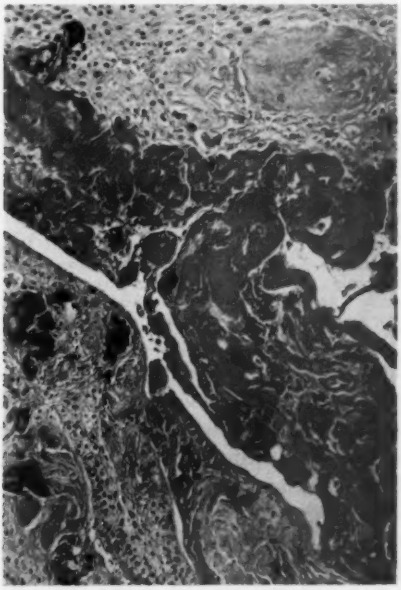

FIG. 5. *Neuropathic arthropathy.* Fibrin, calcific deposits, and proliferation of synovium. ×110.

inflammatory reaction accompanying the urate deposits was usually quite pronounced. In at least two instances the changes were similar to those seen in rheumatoid arthritis.

Miscellaneous Diseases

The correlation of clinical and histopathologic data in this group of miscellaneous diseases is summarized in table 5. Several items are worthy of note. In the group with rheumatic fever, only one patient showed clinical evidence of active inflammation of the knee joint at the time of biopsy, and in this case the findings were those of acute synovitis, nonspecific. None of the

Table 5

Miscellaneous Diseases

Correlation of Clinical and Histopathologic Data

Clinical Diagnosis	Histologic Changes				
	ND	SNS	?RA	RA	Other
Rheumatic fever (6)	5	1	—	—	—
Psychophysiologic musculoskeletal reaction (5)	5	—	—	—	—
Multiple myeloma (4)	4	—	—	—	—
Degenerative joint disease (4)	1	2	1	—	—
Hemochromatosis (3)	1	1	—	—	1*
Charcot's joint (3)	1	—	—	—	2†
Psoriasis (3)	—	1	1	1	—
Sickle cell anemia (2)	2	—	—	—	—
Reiter's syndrome (2)	1	1	—	—	—
Undiagnosed disease (8)	4	2	—	1	1‡

ND = No disease.
SNS = Synovitis, nonspecific.
?RA = Questionable rheumatoid arthritis.
RA = Rheumatoid arthritis.

* Histologic diagnosis of hemochromatosis.
† Histologic diagnosis of Charcot's joint.
‡ Histologic diagnosis of scleroderma.

One case each, xanthomatosis, ulcerative colitis, pseudoxanthoma elasticum, post-traumatic synovitis, lymphopathia venerea, intermittent hydrarthrosis, hypertrophic osteoarthropathy, Darier-Roussy sarcoid, chronic osteomyelitis, chronic lymphatic leukemia, sensitivity to hydrocarbon, and localized scleroderma.

more distinctive features of rheumatoid arthritis was observed. Two of the three specimens from patients with neuropathic arthropathy (Charcot's joints) presented histologic changes (fibrosis, focal calcifications) considered to be characteristic of this disorder.[19] One of the three biopsy specimens from cases of psoriatic arthritis was placed in the category of *rheumatoid arthritis,* another in the *questionable rheumatoid arthritis* group. These observations are in accord with those of Sherman,[20] who believes that the histologic findings in the synovium of psoriatic arthritis are indistinguishable from those encountered in rheumatoid arthritis. In one of

three cases of hemochromatosis there were deposits of finely particulate iron-containing pigment, confined to the surface lining cells, a finding considered to be useful in the differentiation of this form of hemosiderosis from that encountered as a result of hemarthrosis.[21] Hemosiderin-laden macrophages were seen in small numbers in at least 15 other cases, but no correlation with specific disease states was evident. There was no consistent histologic pattern in the four biopsy specimens from patients with degenerative joint disease (osteoarthritis) or any of the other miscellaneous categories listed in table 5.

Summary

The examination of synovium obtained at autopsy examination of patients clinically free of joint disease provided the basis for subsequent histologic study of synovium taken from 136 patients with various rheumatic disorders by means of the punch biopsy procedure of Polley and Bickel. Histologic changes encountered in the necropsy material, and labeled as *sclerotic atrophy*, are believed to be related to aging.

While characteristic pathologic changes were encountered in a majority of patients with active rheumatoid arthritis, these did not prove to be specific, being noted as well in cases of systemic lupus erythematosus and psoriatic arthritis. Marked hyaline thickening, atrophy and vascular sclerosis of the synovium were observed in a number of patients with progressive systemic sclerosis (diffuse scleroderma), and are changes which appear to be pathognomonic of this disease. While urate deposits were detected in the synovium of a number of patients with long-standing gout, the lack of these in many patients with well documented disease (including several with acute gouty geniculitis at the time of biopsy) suggests that tophaceous matter per se plays little part in the development of acute gouty arthritis.

Punch biopsy of the synovium has proved to be a simple, safe and practical procedure which may supply information of considerable value in the study and diagnosis of joint disease.

Acknowledgment

The authors wish to express their appreciation to Miss Margaret E. Swartwood for her skillful histologic preparation of the punch biopsy specimens.

Summario in Interlingua

In despecto del intensificate interesse clinic in le disordines rheumatic, il existe pauc information concernente le natura de alterationes synovial in quasi omne excepte le plus commun formas de morbo articular, proque le articulationes es frequentemente negligite al necropsia, e biopsias ab articulationes aperte non es extensemente in uso. In le presente studio, le examine de synovio obtenite al necropsia ab patientes clinicamente libere de morbo articular esseva usate como base pro le subsequente investigation histologic de synovio obtenite ab 136 patientes con varie disordines rheumatic per medio del technica de biopsia punceate de Polley e Bickel. Ben que characteristic

alterationes pathologic esseva incontrate in un majoritate del patientes con active arthritis rheumatoide, istos non se provava specific: illos habeva etiam essite notate in casos de systemic lupus erythematose e arthritis psoriatic. Marcate grados de spissification, de atrophia, e de sclerosis vascular del synovio esseva observate in un numero de patientes con progressive sclerosis systemic (scleroderma diffuse). Il pare que illos es alterationes que es pathognomonic pro iste morbo. Durante que depositos de urato esseva detegite in le synovio de un numero de patientes con gutta de longe duration, le absentia de tales in numerose patientes in qui le presentia del morbo esseva ben documentate—incluse plures con acute geniculitis guttose al tempore del biopsia—suggere que materia tophacee per se ha un pauco significative rolo in le disveloppamento de acute arthritis guttose.

Biopsia punceate del synovio se ha provate un simple, salve, e practic technica que es capace de provider informationes de considerabile valor in le studio e le diagnose de morbos articular.

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ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY LOCALIZED HYPOTHALAMIC STIMULATIONS * †

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The background of our present knowledge of neurocardiac relationships has previously been summarized.[1, 2, 3] The exact location of the diencephalic structures capable of influencing the electrocardiogram has heretofore not been determined. The investigation presented here was aimed at clarifying the possible role of the hypothalamus in the genesis of some electrocardiographic configurations of clinical interest.

Methods

In the present study the hypothalamus of the cat was explored throughout by means of the Horsley-Clarke apparatus. Three hundred seventy-five individual diencephalic points were electrically stimulated in 10 animals. The location of each point stimulated by the tip of the electrode was in all cases precisely defined by millimeter coördinates. Histologic verification of the electrode placements was accomplished by sectioning and staining the hypothalamus after each experiment. Ether anesthesia was employed for surgery, on termination of which intravenous curarization with Flaxedil and thorough procaine local anesthesia were given and maintained throughout the experiment. Concentric bipolar electrodes were used. The stimulation of each explored point lasted 30 seconds. The stimulus was a square wave current of 3 milliseconds pulse duration and 100 cycles per second, and did not exceed a maximum of 5 volts. These stimulation parameters were found to be most effective for the production of the changes observed. Continuous electrocardiographic tracings were taken in Lead II, using needle electrodes. A control electrocardiogram was run before each stimulation, and a period of recovery elapsed before another site in the hypothalamus was stimulated.

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Results

Stimulation of various locations in the hypothalamus resulted in electrocardiographic manifestations. The majority of the changes observed were elicited by stimulation of the posterior and lateral regions of the hypothalamus. Wave components, rate, rhythm and pacemaker location were found to be susceptible to change by central stimulation. Relative sinus tachycardia was much more frequently observed than bradycardia as a consequence of hypothalamic stimulation. When sinus bradycardia could be elicited, it usually occurred late during stimulation or immediately following stimulation.

Ventricular paroxysmal tachycardia was a frequent result of stimulation of the posterolateral hypothalamus. The sequence of events leading in certain instances to multifocal or unifocal ventricular tachycardia is initiated by a uniform increase in the size of the T wave. The increasing T wave may progress to become the upright component of the biphasic QRS, and the P wave is seen to merge with the QRS (figure 1).

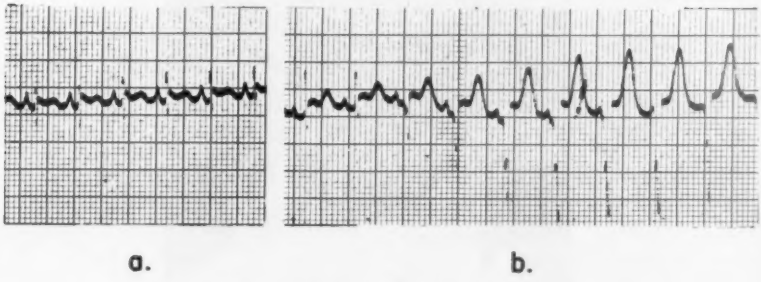

Fig. 1. a. Control. b. 17 seconds after start of stimulation.

A-V dissociation may occur at times. When it occurs and the ventricular rhythm remains regular, the auricular rhythm is usually regular. At onset of the dissociation the P-P interval may increase and then decrease, causing the P wave originating from a pseudonodal focus to wander on the QRS (figure 2d). This type of dissociation is more often seen in the late or poststimulation phase. Early during stimulation the accentuated T may obliterate the P wave, causing prematurity and irregular ventricular rhythm. In figure 3, following stimulation, the pacemaker is seen to step up from ventricle to node and then to its normal sinus locus. Energy transfer from hypothalamus to myocardium is capable of instituting several irritable foci. Sometimes a superimposed pacemaker in the ventricle flickers (figure 4) from one site to another in an orderly fashion. Thus we may have multifocal irregular ventricular rhythm, unifocal regular ventricular rhythm (figure 1), or multifocal ventricular regularity. The latter may take the

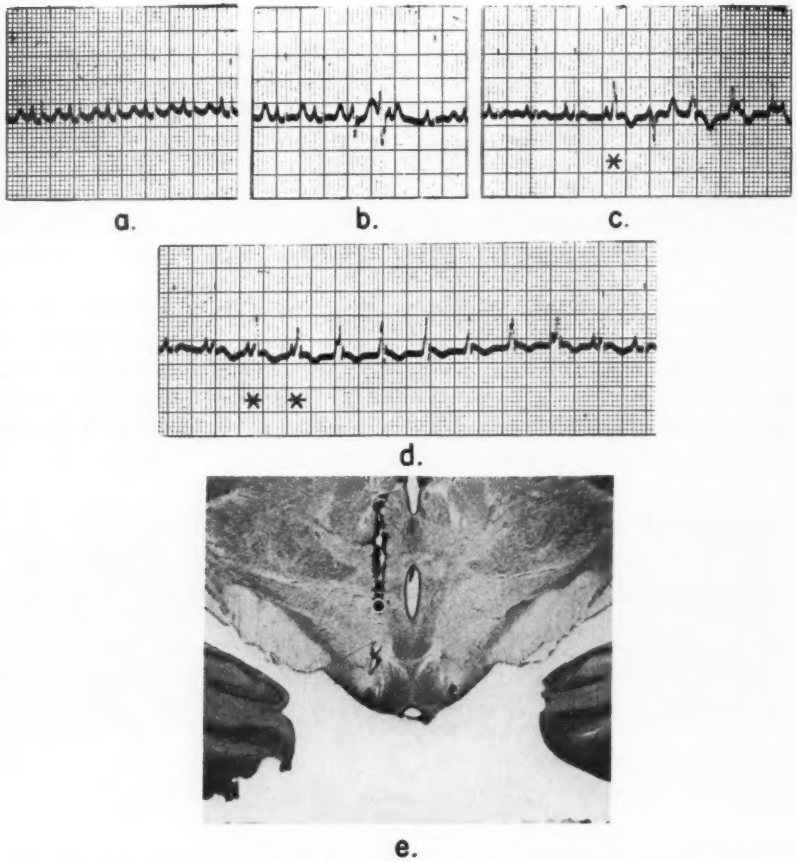

FIG. 2. a. Control. b. 7 seconds after start of stimulation. c. 2 seconds after cessation of stimulation. d. 23 seconds after cessation of stimulation. e. Section of the posterior hypothalamus. The point stimulated is marked by dot.

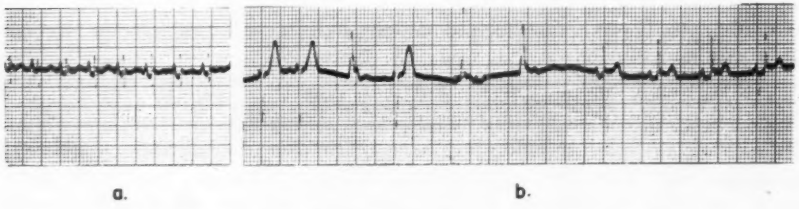

FIG. 3. a. Control. b. Immediately after cessation of stimulation.

form of a normal beat, followed by a unifocal ventricular beat (figure 5b), a type of sequence commonly seen clinically in cases of psychogenic bigeminy.

Apparently, at onset of hypothalamic stimulation, the lower nodal or ventricular pacemaker is too weak to effect more than an alternation with the sinus node, resulting in bigeminy. Later, the ectopic pacemaker takes

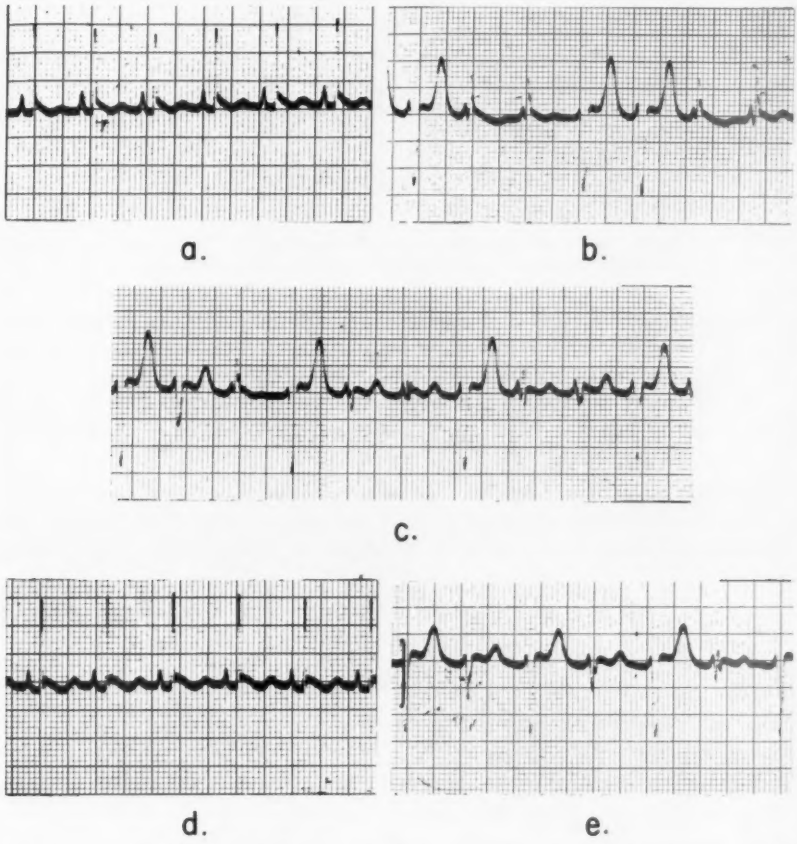

FIG. 4. a. Control (for b and c). b. 26 seconds after start of stimulation. c. Immediately after cessation of stimulation. d. Control (for e). e. 42 seconds after cessation of stimulation.

over completely, or in partnership with other ventricular foci. Two ventricular foci may act alternately (figure 4e), or each of two foci may regularly and alternately cause two consecutive contractions of the heart (figure 4b), or a normal sinus focus and a ventricular focus may set up a trigeminy and a trigeminy-bigeminy (figure 5b), or a quadrigeminy. Figures 6b and 6d show spindle formations of different lengths occurring in a unifocal ven-

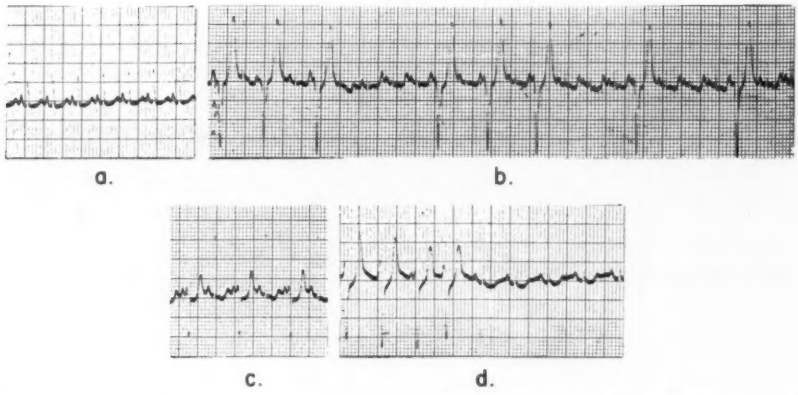

FIG. 5. a. Control. b. 12 seconds after start of stimulation. c. 17 seconds after start of stimulation. d. 9 seconds after cessation of stimulation.

tricular tachycardia during stimulations in adjacent posterior hypothalamic loci. At another locus in the same animal (figure 6f), alternations in size of the S waves occur within a spindle during stimulation.

A reduction in the QRS voltage is sometimes observed after central electrical stimulation. More often, however, an increase in QRS voltage

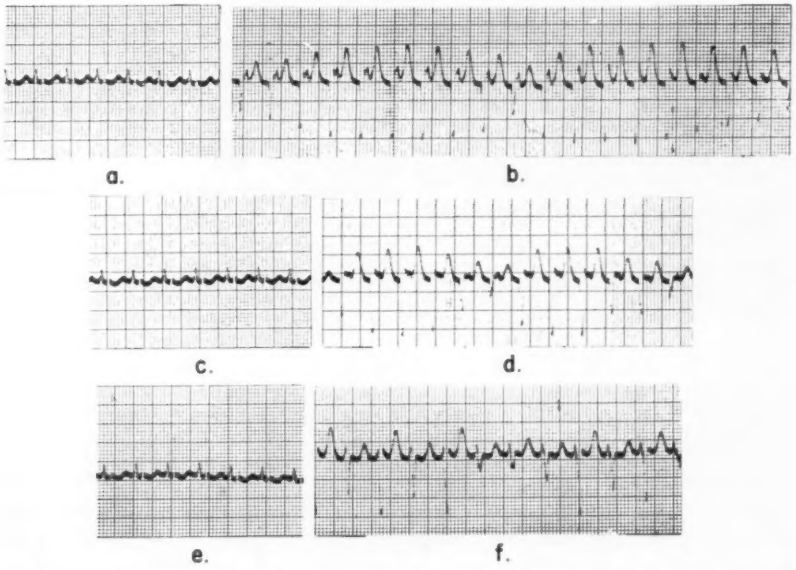

FIG. 6. a. Control (for b). b. 17 seconds after start of stimulation. c. Control (for d). d. 17 seconds after start of stimulation. e. Control (for f). f. 11 seconds after start of stimulation.

results. Repolarization may be affected variously. An ST elevation, or an inversion of the T wave, may be observed during stimulation. A well defined U wave was encountered in three instances during and after stimulation, two of the loci stimulated being in the anterior and one in the posterior hypothalamus.

P wave changes and auricular extrasystoles were not common, although they occurred in some instances. Elevation of the P wave was minor in the few cases in which it was observed. Marked diminution of the P was seen at times in conjunction with a late nodal rhythm (figure 3), where normal P impulse formation was completely suppressed. When A-V dissociation occurred together with irregular multifocal ventricular rhythm (figure 2), P waves were irregular in both amplitude and rhythm.

The alterations in the duration of P-R and QRS intervals were analyzed for their possible interest in relation to the pathogenesis of the Wilson-Wolff-Parkinson-White syndrome. It may be seen in the control record of figure 2a that the P-R interval is 0.08 sec. and the QRS interval is 0.03 sec. During and following one-half minute of electrical stimulation in a locus in the posterior hypothalamus, A-V dissociation occurs. One observes a pseudonodal focus, a wandering sinus pacemaker (figure 2d), and initial nodal beats (three beats are starred) in which P-R is now 0.07 sec. and QRS is 0.05 sec. The configurations may simulate right bundle branch block, placing these beats within the criteria of classification in the Wilson-Wolff-Parkinson-White syndrome. When the electrode was shifted 3 mm. in the hypothalamus and the same electrical stimulus was applied, a remarkable sequel occurred in which *alternate* beats exhibited a narrowing of the PR interval, a widening of the QRS interval, and T inversion. When the electrode tip was shifted another millimeter and another stimulation was effected, the bigeminal effect faded and the phenomenon of shortening of P-R, broadening of QRS and T inversion was most striking every fourth beat. This grouping of effects was not uncommon in our series of experiments. At times the P wave was seen on the ascending limb of the QRS complex, another type of Wilson-Wolff-Parkinson-White phenomenon as classified by Öhnell.[11]

In control experiments, Flaxedil, injected intravenously, in no instance resulted in electrocardiographic change. Intravenous pentobarbital was found to block the hypothalamic electrical stimulatory effects on the electrocardiogram.

Discussion

The variety of electrocardiographic manifestations in this study indicates the complexity of the control exerted by the hypothalamus upon the heart, a complexity perhaps not fully apprehended in previous investigations bearing upon the problem.[7, 15, 16, 17] The pathways involved in the transmission of

the stimulus from the hypothalamus to the heart muscle are probably those described by Beattie et al.[16] Cardiac effects obtained in the present study late during stimulation, or after stimulation had ceased, may be reflex phenomena, involving the medulla and other cardioregulatory centers. The secondary effects are often cardio-inhibitory (figure 3), and frequently include runs of nodal rhythm.

Because distortion or inversion of the P wave was not seen, except by encroachment of an enlarging T wave, it may be inferred that the preponderant influence flows from hypothalamus to the ventricular myocardium. Often the vicinity of the A-V node appears to be heavily affected. The very early occurrence of adventitious foci, manifest by irregularities in the T wave and the common early enlargement of the T wave, might lead to the presumption that the occasional concurrent auricular extrasystoles could involve a retrograde phenomenon. The reduction in the voltage of the QRS complex, which we have observed to follow some stimulation, does not seem to be the result of myocardial fatigue. The phenomenon resembles that which occurs after injection of quinidine into the third cerebral ventricle.[8] It is also known to follow clinical quinidine excess.

Areas of greatest sensitivity in production of cardiac effects were found generally in the posterior and lateral hypothalamus. More extensive details of anatomic localization in the brain will be treated in another publication.[18] The same areas were reported by Manning and Peiss [8] and Rushmer and Smith [9] to increase myocardial contractility when stimulated. The electrocardiographic manifestations may be classified as initial or secondary, depending upon the time of appearance after onset of diencephalic stimulation. The initial effects, seen early during stimulation, frequently included wave augmentation, QRS amplitude change, extrasystoles principally from nodal and ventricular foci, and runs of (pseudo) nodal and ventricular tachycardia. The secondary effects, such as relative bradycardia, rhythmic grouping and pacemaker shifts, including the Wilson-Wolff-Parkinson-White phenomenon, were probably the result of delayed reflex activation of accessory cardioregulatory centers within the nervous system.

Within the initial group we may see both irregular (multifocal) and regular (unifocal) ventricular rhythm with varying degree of A-V dissociation. One cannot therefore differentiate between a "true" and a "pseudo" ventricular tachycardia on the basis of the regularity of the rhythm. The observations in the present study would appear to support, within the limits imposed by species difference, the conclusion of Schrire and Vogelpoel [10] that, if the QRS is of normal duration, the tachycardia is supraventricular. However, in the bidirectional type of "pseudo" ventricular tachycardia, with a slurred S-T segment (figure 5d), the QRS dimension is not easily apparent, and where preëxcitation occurs (figure 2), a bundle branch block may be simulated. The duration of the QRS may also be indistinct where the P wave, in a wandering pacemaker sequence, is superimposed upon the

S-T segment (figure 6), a pattern likely to be mistakenly called "retrograde conduction."

The records were analyzed for criteria bearing upon possible extracardiac etiology of the Wilson-Wolff-Parkinson-White syndrome, or as designated by Hejtmancik and Herrmann,[6] the electrocardiographic syndrome of short P-R interval and broad QRS complexes. The progressive shortening of the P-R interval appears to be a form of centrally controlled dissociation, and it is interesting to note in this connection that Wolff et al.,[12] as well as Fenichel,[13] felt that both the short PR and the QRS block of the much discussed Wilson-Wolff-Parkinson-White syndrome were due to the influence of extracardiac nerves. The capability of a single hypothalamic site to produce the Wilson-Wolff-Parkinson-White phenomenon associated with paroxysmal tachycardia is of significance, as Hejtmancik and Herrmann have demonstrated,[6] the clinical association of the Wilson-Wolff-Parkinson-White syndrome and paroxysmal arrhythmias is quite common. Furthermore, organic heart disease is often absent in the Wilson-Wolff-Parkinson-White syndrome.

Our investigation supports the contention of Ranson [4] that the hypothalamus is devoid of parasympathetic centers, though possibly not of parasympathetic pathways from the "prehypothalamus," and that the posterior hypothalamus may be considered to contain a sympathetic center or centers. The concept of anterior hypothalamic cardiovascular inhibition, balanced by posterior hypothalamic stimulatory function, receives only weak corroboration. One would expect to produce primary sinus inhibition with bradycardia or standstill if the anterior hypothalamus contained cardioinhibitory centers. Bradycardia, when present, occurred late in stimulation or after stimulation, presumably from activation of other areas within the central nervous system, perhaps the same areas which produce prolonged cardiac standstill during encephalography.[14]

There is evidence indicating that sympathetic and possibly also the parasympathetic nerve fibers reach all parts of the heart,[2] largely by accompanying the blood vessels. However, the intracardiac mechanisms resulting in the electrocardiographic changes observed in our experiments have not been determined.

Summary

Through the use of the Horsley-Clarke technic in a series of cats the hypothalamus was explored by means of electrical stimulations and simultaneous electrocardiographic recordings. The manifestations, obtained by stimulation of histologically confirmed points, chiefly in the lateral and posterior hypothalamus, included marked alterations in the wave components QRS and T, changes in rhythm such as bigeminy and trigeminy, A-V dissociation, extrasystoles, paroxysmal nodal and ventricular tachycardias, and the Wilson-Wolff-Parkinson-White configuration.

ACKNOWLEDGMENTS

We are indebted to the Department of Biophysics, and specifically to Professor A. W. Bellamy and Professor M. Verzeano, for technical advice and for making available some of their facilities.

SUMMARIO IN INTERLINGUA

Le objectivo del presente studio esseva determinar qual areas del mesencephalo es possibilemente de signification predominante in le genese de specific configurationes electrocardiographic e de anormal rhythmos cardiac que es de interesse clinic. Tal areas in le cerebro ha non usque nunc essite identificate, ben que on ha studiate relationes neuro-cardiac depost multe annos e ab varie punctos de vista.

Con le uso del technica de Horsley-Clarke, 375 histologicamente confirmate punctos diencephalic esseva stimulate electricamente in un serie de cattos, e le effectos electrocardiographic de ille stimulation esseva registrate. Iste effectos—veniente primarimente ab areas in le hypothalamo lateral e posterior—includeva tachycardias sinusal, nodal, e ventricular, marcate alterationes del voltage e del conformation de componentes undal in QRS e T, dissociation atrio-ventricular, alterationes del rhythmo (tal como bi- e trigeminia), e un configuration simile a illo describite per Wilson, Wolff, Parkinson, e White.

Le resultatos indica que le hypothalamo postero-lateral exerce un profunde influentia super le stato functional del myocardio. Phenomenos de dissociation atrio-ventricular resultante ab le stimulation electric del diencephalo pare intrainar le concomitante excitation de altere areas in le systema nervose, con un inhibition reflexe del nodo sinusal.

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CHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE: A COMPARATIVE STUDY OF THEIR HYPOTENSIVE, SALURETIC AND HYPERURICEMIC ACTION * †

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INTRODUCTION

THE synthesis of chlorothiazide by Novello and Sprague [1] and the discovery of its favorable saluretic action [2, 18, 19] introduced a unique type of pharmaceutic agent to the management of cardiovascular diseases. Chlorothiazide (Diuril), a heterocyclic sulfonamyl compound (figure 1A) is an orally effective diuretic, useful in the treatment of congestive heart failure and other edematous conditions. In addition, this drug has some antihypertensive properties, and usually augments the antihypertensive activity of sympathetic depressor agents. It has been claimed that chlorothiazide, by virtue of its activity as a carbonic anhydrase inhibitor, induces natruresis and kaluresis, and causes the excretion of an alkaline urine containing bicarbonate.[3, 4] Chlorothiazide also induces natruresis and chloruresis in a manner analogous to that of mercurial diuretics, blocking the reabsorption of sodium and chloride ions.[4]

Hydrochlorothiazide (Hydrodiuril) is the dihydro derivative of chlorothiazide. It is a potent saluretic agent that resembles chlorothiazide qualitatively, but has been claimed to be several times more active quantitatively.[11] Chemically, hydrochlorothiazide differs from chlorothiazide in having no double bonds in the heterocylic ring (figure 1B). It has been reported that the primary action of this drug is to decrease the renal tubular reabsorption of sodium and chloride, and that the urinary loss of potassium and bicarbonate is relatively less than that seen with chlorothiazide.[6]

To compare the natruretic, kaluretic and hypotensive action of this compound with that of chlorothiazide, a double-blind clinical trial was carried out. The objectives of the study were to investigate the results of oral administration of these two compounds on systolic and diastolic blood pres-

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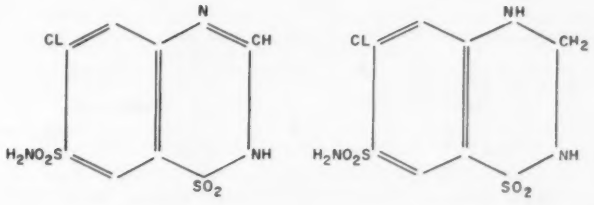
sure, serum and urine electrolytes, urine volume and total body weight of hypertensive patients. Since it has been reported previously that the administration of chlorothiazide may be associated with hyperuricemia,[13, 14] it was also decided to compare the effect of these drugs on serum uric acid concentration.



CHLOROTHIAZIDE (DIURIL) HYDROCHLOROTHIAZIDE (HYDRODIURIL)

FIG. 1. A (*left*). Chemical structure of chlorothiazide. B (*right*). Chemical structure of hydrochlorothiazide.

METHODS AND MATERIALS

A group of 24 patients was selected from the Hypertension Clinic. They were diagnosed as having "chronic hypertensive cardiovascular disease," [7] with sustained elevation of systolic and diastolic blood pressure, cardiac hypertrophy (electrocardiography and chest x-ray), and hypertensive retinopathy. All of the patients had a history of congestive heart failure and were receiving digitalis preparations daily, but they were not edematous. As for the etiology of hypertension in these patients, some had no demonstrable cause, and were diagnosed by exclusion as "essential hypertension," while in some the malady was thought to be on the basis of chronic renal disease. Table 1 summarizes the distribution of these patients by age, sex, race and the etiology of the disease, renal or essential hypertension.

Since all of the patients were selected from the Hypertension Clinic and were on various antihypertensive treatment schedules, it was decided to withhold all of the antihypertensive drugs on each patient for two weeks prior to the start of the investigation. Other than the test drugs the patients received no treatment during the course of the study except for digitalis preparations.

The "double-blind" study was designed to compare two different dose levels of chlorothiazide (500 and 1,000 mg. per day), two dose levels of hydrochlorothiazide (50 and 100 mg. per day),* and a placebo. For this purpose five different kinds of tablets, looking exactly alike in every respect,

* The usually recommended oral dosage for chlorothiazide is either 500 or 1,000 mg. per day; for hydrochlorothiazide, it is either 50 or 100 mg. per day. For this reason, the above-mentioned dose levels were used.

were manufactured.* They were coded by the manufacturing laboratory using three different five-digit numbers for each tablet (i.e., placebo = 14918, 14876, 14865, etc.). The tablets were placed in small bottles containing 20 tablets each. Each bottle was identified by one of these numbers. A different code number was used each time a specific drug was given to a

TABLE 1

Distribution of the 23 Hypertensive Patients as to Age, Sex, Race and the Etiology of the Disease

Age Group	Essential Hypertension*				Renal Disease				Total
	White		Nonwhite		White		Nonwhite		
	Males	Females	Males	Females	Males	Females	Males	Females	
35–39				1					1
40–44				2				1	3
45–49			4	3				2	9
50–54			2	2			2	2	8
55–59	1		1						2
Total	1		7	8			2	5	23

* Diagnosed by exclusion.

patient, so that physicians using the drugs could not, unintentionally, introduce a bias into the study. The patients using the drug did not know the nature of the "pills" they were taking. The study was designed in such manner that each patient received a specific tablet twice a day for two consecutive weeks, followed by a week without therapy except digitalis. Each patient received all of the different tablets during the course of the investigation, but the order of administration of each drug differed from individual to individual. For this purpose, a plan was arranged for 24 different treatment schedules, each containing placebo, two doses of chlorothiazide and two doses of hydrochlorothiazide.

Each of the 24 patients was randomly allotted one of the 24 treatment schedules. For this, the "ten thousand randomly assorted digits" from the tables by Snedecor [8] were used (table 2).

Each treatment schedule contained five different treatments; therefore, five different cardboard boxes were provided for each patient, each containing a specific drug supply for two weeks. The name of the patient and the order of the administration of each treatment was written on the top of each box, and all of the boxes were sealed. Each patient was given a box at the start of each treatment period and was told to return the remainder of the tablets in each box at the end of every two-week treatment period, to assure that he had been taking the tablets regularly and as directed. The patients

* The tablets were made available by Merck, Sharp and Dohme Laboratories through the courtesy of Dr. Elmer Alpert.

visited the clinic at the end of each week, at which time the total body weight was recorded and a complete physical examination was performed. Blood pressures were determined in the recumbent position at three different intervals (at the start of the examination, and at five-minute and 10-minute intervals), using the same sphygmomanometer for each patient throughout the study. The three different readings thus obtained were used in final analysis of each week of observation. The patients were instructed in the method of collection of a 24-hour urine specimen. The volume of the urine specimens thus collected was measured at each clinic visit, and a sample

TABLE 2

Randomly Assorted 24 Treatment-Schedules to 24 Patients

(For details, see the text in "Methods and Materials")

Treatment Schedules	Drugs	Patient Number	Treatment Schedules	Drugs	Patient Number
1	A-B-C-D-E	10	13	B-A-C-D-E	17
2	A-B-E-C-D	23	14	B-A-E-C-D	4
3	C-D-E-A-B	8	15	C-D-E-B-A	5
4	E-C-A-D-B	22	16	E-C-D-B-A	14
5	E-A-B-C-D	11	17	E-B-A-C-D	1
6	C-D-A-B-E	9	18	C-D-B-A-E	20
7	A-B-D-C-E	2	19	B-A-D-C-E	18
8	A-B-E-D-C	16	20	B-A-E-D-C	12
9	D-C-E-A-B	6	21	D-C-E-B-A	15
10	E-D-C-A-B	21	22	E-D-C-B-A	24
11	E-A-B-D-C	3	23	E-B-A-D-C	7
12	D-C-A-B-E	19	24	D-C-B-A-E	13

Key: A = Placebo; B = Hydrodiuril, 50 mg.; C = Diuril, 250 mg.; D = Diuril, 500 mg.; E = Hydrodiuril, 25 mg.

of this specimen, in a securely sealed plastic container, was sent to the chemistry laboratory of the hospital for the determination of the 24-hour urinary excretion of sodium and potassium. At the same time, blood was drawn in standard laboratory test tubes and was sent to the laboratory for the chemical determinations of serum sodium, potassium and uric acid concentration. The serum sodium and potassium was determined by flame photometer; the serum uric acid was determined by the Archibold method (a modification of the Kern and Strausky method). Two laboratory technicians were assigned to do the determination of serum and urine electrolytes. If the determinations were not done on the same day the specimen was collected, it was kept in a refrigerator at 4° C. for the day of analysis. To collect urine for uric acid determination, it was necessary to add some chemical preservative agents to preserve the uric acid, which was not practical, and it was decided to determine only sodium and potassium excretion in the urine.

The observation period lasted 17 weeks, including one week without therapy between each treatment period, as well as two weeks at the start and one week at the end of the study. One of the patients was dropped

from the study during the course of the investigation because she did not attend the clinic regularly and therefore was not considered to be reliable in following the instructions properly. The remaining 23 patients participated in the study without any complication.

The data were punched into IBM cards and then fed into an IBM "sorter" and "compiler," from which a printed listing of the data in order of placebo, chlorothiazide (two different doses), and hydrochlorothiazide (two different doses) was obtained. Since the patients received the treatment schedules at random, and since the order effect of each treatment schedule was not a major problem, it was decided to perform the statistical analysis of the data using the classic "two way analysis of variance."[8,9] The significance of the F ratio thus obtained was tested with the standard F ratio tables at the probability levels of 0.001, 0.01 and 0.05.[8,9] If the F ratio obtained from the analysis of variance was significant at the probability level of 0.001 or 0.01, a further analysis was performed to compare the means of the two different observations and to test the significance of the differences between the two means. To circumvent the difficulties in determining the significance in multiple "t" testing, the means were compared by the method described by Scheffé,[10] which also enables one to compare all possible means. In this method, confidence limits are computed for the difference between the two means to be compared by the use of the formula:

$$\pm \sqrt{(k-1)F\,\alpha(k-1,N_2)}\sqrt{\frac{Mswg}{r_1}+\frac{Mswg}{r_2}}$$

where $k-1$ = degrees of freedom of the numerator of the F ratio obtained in analysis of variance; N_2 = degrees of freedom of the denominator of the F ratio obtained in analysis of variance; α = the level of probability for the F ratio (0.001, 0.01 or 0.05, etc.); $Mswg$ = mean squares of interaction between individuals and the drugs (derived from analysis of variance); r_1 and r_2 = numbers of subjects in each of the two groups to be compared. Here $r_1 = r_2 = 23$.

Where there is a significant difference between two means at α probability level, the confidence limits of the difference do not include zero.

Results

The results of all of the observations are summarized in table 3.

Effect of Chlorothiazide and Hydrochlorothiazide on Systemic Blood Pressure:

1. *Diastolic blood pressure.* The diastolic blood pressure was lowered with chlorothiazide and hydrochlorothiazide (table 3). Although the reduction in diastolic blood pressure was not consistent in every patient, the analysis of variance of the changes in the mean diastolic blood pressure re-

TABLE 3

Means and Standard Errors of the Means of Observed Parameters in Hypertensive Patients on Different Drug Schedules

Parameter	Placebo	Chlorothiazide ("Diuril") 250 mg. b.i.d.	Chlorothiazide ("Diuril") 500 mg. b.i.d.	Hydrochlorothiazide ("Hydrodiuril") 25 mg. b.i.d.	Hydrochlorothiazide ("Hydrodiuril") 50 mg. b.i.d.
Diastolic B.P. (mm.Hg)	124.91 ±2.84*	115.05 ±2.38	116.33 ±3.14	116.45 ±3.06	117.29 ±2.74
Systolic B.P.	209.05 ±6.24	184.73 ±5.30	188.49 ±6.75	186.27 ±6.61	185.72 ±6.17
Weight (lbs.)	160.17 ±7.14	157.60 ±7.00	157.39 ±6.99	157.47 ±7.05	156.97 ±7.02
Serum Na (mEq./L.)	151.17 ±0.642	150.93 ±0.531	150.86 ±0.558	150.50 ±0.660	151.08 ±0.679
Serum K (mEq./L.)	4.49 ±0.127	4.42 ±0.141	3.96 ±0.134	4.06 ±0.118	3.86 ±0.121
Serum U. A. (mg.%)	6.64 ±0.373	7.82 ±0.406	7.87 ±0.429	8.11 ±0.450	8.39 ±0.410
Urine volume (liter)	1.55 ±0.08	1.43 ±0.09	1.53 ±0.08	1.51 ±0.07	1.53 ±0.07
Urine Na (mEq./L.)	107.32 ±10.27	110.19 ±8.14	105.17 ±7.15	111.31 ±8.13	112.30 ±10.02
Urine K (mEq./L.)	35.59 ±3.90	38.26 ±4.29	35.40 ±3.85	39.10 ±3.99	34.77 ±3.16

* Standard error of the mean.

sulted in an F ratio of 8.43, which was highly significant ($P < 0.001$). The mean diastolic blood pressure during the placebo period was 124.91 mm. Hg, which was reduced to 117.29 mm. Hg with hydrochlorothiazide, 50 mg. twice a day, and to 115.05 mm. Hg with "Diuril," 250 mg. twice a day, and to 116.33 with "Diuril," 500 mg. twice a day, and finally to 116.45 with "Hydrodiuril," 25 mg. twice a day. There was no significant difference between the effects of two different doses of each drug (chlorothiazide and hydrochlorothiazide) on the diastolic blood pressure of these patients (table 4).

2. *Systolic blood pressure.* The systolic blood pressure was also lowered with both chlorothiazide and hydrochlorothiazide (table 3). The analysis of variance of this reduction of the systolic blood pressure resulted in an F ratio of 16.641, which was highly significant ($P < 0.001$). The

TABLE 4

Comparison of Mean Diastolic Blood Pressures in 23 Hypertensive Patients on Different Therapeutic Regimes

(Method of Scheffé, 1953)

Drugs Compared	Range of the Confidence Limit (Per Cent)	Differences of the Mean	Confidence Limit of the Difference	
			Upper	Lower
Placebo and Hydrodiuril, 50 mg. b.i.d.	99	7.62	+14.60	+0.64*
Placebo and Diuril, 250 mg. b.i.d.	99.9	9.86	+18.43	+1.283†
Placebo and Diuril, 500 mg. b.i.d.	99.9	8.58	+17.15	+0.01†
Placebo and Hydrodiuril, 25 mg. b.i.d.	99	8.46	+15.44	+1.48*
Hydrodiuril, 50 mg., and Diuril, 500 mg.	95	0.96	+6.86	−4.94
Hydrodiuril, 25 mg., and Hydrodiuril, 50 mg.	95	0.84	+6.74	−5.06
Diuril, 500 mg., and Diuril, 250 mg.	95	1.28	+7.18	−4.62
Hydrodiuril, 25 mg., and Diuril, 250 mg.	95	1.40	+7.30	−4.50
Hydrodiuril, 50 mg., and Diuril, 250 mg.	95	2.24	+8.14	−3.66
Diuril, 500 mg., and Hydrodiuril, 25 mg.	95	0.12	+6.02	−5.78

* Significant $P < 0.01$.
† Significant $P < 0.001$.

mean systolic blood pressure during the placebo period was 209.05 mm. Hg, which became 188.49 mm. Hg with "Diuril," 500 mg. twice a day, and 184.73 mm. Hg with "Diuril," 250 mg. twice a day, and 185.72 mm. Hg with "Hydrodiuril," 50 mg. twice a day, and finally 186.27 mm. Hg with "Hydrodiuril," 25 mg. twice a day. The differences between the mean systolic blood pressure during the chlorothiazide and hydrochlorothiazide therapy period and the placebo period were highly significant (table 5), but there was no significant difference in the effect of chlorothiazide on systolic blood pressure as compared with that of hydrochlorothiazide. Furthermore, there was no significant difference in the effect of two different doses of each drug on systolic blood pressure.

TABLE 5

Comparison of Mean Systolic Blood Pressure in 23 Hypertensive Patients on Different Therapeutic Regimes

(Method of Scheffé, 1953)

Drugs Compared	Range of the Confidence Limit (Per Cent)	Differences of the Mean	Confidence Limit of the Difference	
			Upper	Lower
Placebo and Hydrodiuril, 50 mg. b.i.d.	99.9	23.33	+39.74	+ 6.91*
Placebo and Diuril, 250 mg. b.i.d.	99.9	24.32	+40.73	+ 7.90*
Placebo and Diuril, 500 mg. b.i.d.	99.9	20.56	+36.97	+ 4.14*
Placebo and Hydrodiuril, 25 mg. b.i.d.	99.9	22.78	+39.19	+ 6.36*
Hydrodiuril, 50 mg., and Diuril, 500 mg.	95	2.77	+14.07	− 8.53
Hydrodiuril, 25 mg., and Hydrodiuril, 50 mg.	95	0.55	+11.85	−10.75
Diuril, 500 mg., and Diuril, 250 mg.	95	3.76	+15.06	− 7.54
Hydrodiuril, 25 mg., and Diuril, 250 mg.	95	1.54	+12.84	− 9.76
Hydrodiuril, 50 mg. and Diuril, 250 mg.	95	0.99	+12.29	−10.31
Diuril, 500 mg. and Hydrodiuril, 25 mg.	95	2.22	+13.52	− 9.08

* Significant $P < 0.001$.

Effect of Chlorothiazide and Hydrochlorothiazide on Total Body Weight: Each patient was weighed with the same scale at the end of each week.

The average change in the total body weight (table 3) in the 23 patients was statistically significant. The analysis of variance of the data yielded an F ratio of 11.53, which was highly significant ($P < 0.001$). Further analysis of this variation in total body weight (according to Scheffé's method) revealed that the reduction of total body weight was significant only when the "placebo period" was compared with any of the four drug schedules (table 6). The mean value for the total body weight during the placebo period was 160.17 pounds. This was reduced to 157.39 pounds with "Diuril," 1,000 mg. per day, to 157.60 with "Diuril," 500 mg. per day, to 156.97 with "Hydrodiuril," 100 mg. per day, and to 157.47 pounds with "Hydrodiuril," 50 mg. per day (table 3).

There was no appreciable difference between two doses of chlorothiazide and two doses of hydrochlorothiazide when their effects on total body weight were compared (table 6).

TABLE 6

Comparison of the Means of Body Weight of 23 Hypertensive Patients on Different Therapeutic Regimes

(Method of Scheffé, 1953)

Drugs Compared	Range of the Confidence Limit (Per Cent)	Differences of the Mean	Confidence Limit of the Difference	
			Upper	Lower
Placebo and Hydrodiuril, 50 mg. b.i.d.	99.9	3.2	+5.58	+0.820*
Placebo and Diuril, 250 mg. b.i.d.	99.9	2.57	+4.95	+0.190*
Placebo and Diuril, 500 mg. b.i.d.	99.9	2.78	+5.16	+0.40*
Placebo and Hydrodiuril, 25 mg. b.i.d.	99.9	2.70	+5.08	+0.32*
Hydrodiuril, 50 mg., and Diuril, 500 mg. b.i.d.	95	0.42	+2.05	−1.21
Hydrodiuril, 50 mg., and Diuril, 250 mg. b.i.d.	95	0.63	+2.26	−1.00
Hydrodiuril, 50 mg., and Hydrodiuril, 25 mg.	95	0.50	+2.13	−1.13
Diuril, 500 mg., and Diuril, 250 mg.	95	0.21	+1.84	−1.42
Diuril, 250 mg., and Hydrodiuril, 25 mg.	95	0.13	+1.76	−1.50
Diuril, 500 mg., and Hydrodiuril, 25 mg.	95	0.08	+1.71	−1.55

* Significant $P < 0.001$.

Effect of Chlorothiazide and Hydrochlorothiazide on Serum Sodium: The serum sodium concentration was measured on each patient at the end of each week. Although there was some reduction in serum sodium in some of the patients, the over-all changes in sodium concentration in all 23 patients were not statistically significant during the drug therapy as compared with the placebo period. The *F* ratio obtained from the analysis of variance of the mean serum sodium concentration was 0.369, which is not significant at the 0.05 level. The mean serum sodium concentration during the placebo period was 151.17 mEq./L., and this did not change much during the period of various forms of therapy (table 3).

Effect of Chlorothiazide and Hydrochlorothiazide on Serum Potassium: The differences in man of serum potassium concentration during the chlorothiazide, hydrochlorothiazide and placebo period in the entire group of 23 patients computed by analysis of variance were highly significant ($P < 0.001$) (table 7). The mean value for serum potassium concentration during the placebo therapy was 4.49 mg.%, and was 3.96 and 4.42 with chlorothiazide (1,000 mg. and 500 mg., respectively). During the hydrochloro-

TABLE 7

Analysis of Variance of Serum Potassium in 23 Hypertensive Patients

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Squares
Individuals	22	25.2078	1.1458
Drugs	4	7.2236	1.8059
Interaction, individuals and drugs	88	16.9064	0.1921

$F = 9.4008$*.

* Highly significant $P < 0.001$.

thiazide therapy there was also a reduction in serum potassium concentration, to 3.86 and 4.06 (100 mg. and 50 mg., respectively). These changes are summarized in table 3.

The reduction of the mean serum potassium concentration during the administration of chlorothiazide and hydrochlorothiazide when compared with the mean serum potassium concentration during the placebo period was greater with the higher dosage of each drug. The higher dose level of hydrochlorothiazide (100 mg. per day) as compared with placebo caused a greater fall in serum potassium ($P < 0.001$) than did the higher dose level of chlorothiazide (1,000 mg. per day) as compared with placebo ($P < 0.01$). The smaller doses of the two drugs also caused some reduction in

TABLE 8

Comparison of Mean Serum Potassium Concentrations in 23 Hypertensive Patients on Different Therapeutic Regimes

(Method of Scheffé, 1953)

Drugs Compared	Range of the Confidence Limit (Per Cent)	Differences of the Mean	Confidence Limit of the Difference	
			Upper	Lower
Placebo and Hydrodiuril, 50 mg. b.i.d.	99.9	0.63	+1.211	+0.049‡
Placebo and Diuril, 250 mg. b.i.d.	95	0.07	+0.4704	−0.3304
Placebo and Diuril, 500 mg. b.i.d.	99	0.53	+1.003	+0.0568†
Placebo and Hydrodiuril, 25 mg. b.i.d.	95	0.43	+0.8304	+0.029*
Hydrodiuril, 50 mg., and Diuril, 250 mg. b.i.d.	99	0.56	+1.033	+0.086†
Hydrodiuril, 50 mg., and Diuril, 500 mg. b.i.d.	95	0.105	+0.5054	−0.2954
Diuril, 500 mg., and Diuril, 250 mg. b.i.d.	95	0.46	+0.8604	+0.059*
Hydrodiuril, 50 mg., and Hydrodiuril, 25 mg. b.i.d.	95	0.205	+0.605	−0.195

* Significant $P < 0.05$.
† Significant $P < 0.01$.
‡ Significant $P < 0.001$.

serum potassium concentration. However, the smaller dose level of chlorothiazide (500 mg. per day) did not produce a significant fall when compared with placebo ($P > 0.05$), while the smaller dose level of hydrochlorothiazide (50 mg. per day) caused a significant fall in serum potassium when compared with placebo ($P < 0.05$) (table 8). Also, when the mean serum potassium concentration during the higher doses of both hydrochlorothiazide (100 mg. per day) and chlorothiazide (1,000 mg. per day) was compared with the mean of serum potassium concentration during the smaller dose of chlorothiazide (500 mg. per day), the significance in the change of the mean serum potassium was greater with hydrochlorothiazide ($P < 0.01$) than with chlorothiazide ($P < 0.05$). Therefore, in the comparison of the means of serum potassium concentration during the period of therapy with two different doses of these drugs and placebo, it was observed that hydrochlorothiazide (in both dose levels) causes a more significant fall in serum potassium than does chlorothiazide. In fact, when the patients were

receiving smaller doses of chlorothiazide (500 mg. per day), there was no significant change in the serum potassium concentration as compared with the mean of serum potassium during the placebo period ($P > 0.05$).

Effect of Chlorothiazide and Hydrochlorothiazide on Serum Uric acid: In all 23 patients the administration of "Diuril" or "Hydrodiuril" was followed by a prompt, consistent and highly significant ($P < 0.001$) rise of the serum uric acid (table 9). The mean value of serum uric acid concentration in all of the patients during placebo therapy was 6.64 mg.%. Serum uric acid concentration in hypertension is currently under investigation. Although with the method used, individual values up to 7.0 mg. per 100 c.c. cannot be considered to be abnormal, the fact that the mean value was 6.64 mg.% and 14 of the 23 patients had values in excess of 7.0 (with normal serum urea nitrogen concentrations) suggests that the possibility of hyperuricemia in hypertension should be investigated. The mean serum uric acid

TABLE 9

Analysis of Variance of Serum Uric Acid of 23 Hypertensive Patients

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Squares
Individuals	22	395.9413	17.9973
Drugs	4	41.1073	10.2768
Interaction, individuals and drugs	88	41.0327	0.4662

$F = 22.04$*.
* Highly significant $P < 0.001$.

rose to 8.39 mg.% with "Hydrodiuril," 50 mg. twice a day, to 7.82 mg.% with "Diuril," 250 mg. twice a day, to 7.87 mg.% with "Diuril," 500 mg. twice a day, and to 8.11 mg.% with "Hydrodiuril," 25 mg. twice a day. These changes as compared with the mean value during placebo therapy were statistically significant ($P < 0.001$) (table 10). However, the changes in the level of serum uric acid, when compared together during the treatment period with two different doses of chlorothiazide (Diuril) and two different doses of hydrochlorothiazide (Hydrodiuril), were not statistically significant at the 5% level ($P > 0.05$) (table 10). Also, the changes in the serum uric acid with two different doses of each drug were not significant ($P > 0.05$) (table 10). The mean value for serum urea nitrogens in all patients before the beginning of the study was 13.6 ± 0.92,* which remained unchanged during the entire course of the study.

Effect of Chlorothiazide and Hydrochlorothiazide on 24-hour Urine Volume and 24-Hour Urinary Excretion of Sodium and Potassium: The 24-hour urine volume as well as the concentration of sodium and potassium per liter of urine was also measured at the end of each week. The 24-hour urine specimen was collected during the last 24-hour period of each week.

* Standard error of the mean.

TABLE 10

Comparison of Mean Serum Uric Acid Concentrations in 23 Hypertensive Patients on Different Therapeutic Regimes

(Method of Scheffé, 1953)

Drugs Compared	Range of the Confidence Limit (Per Cent)	Differences of the Mean	Confidence Limit of the Difference	
			Upper	Lower
Placebo and Hydrodiuril, 50 mg. b.i.d.	99.9	1.75	+2.644	+0.855*
Placebo and Diuril, 250 mg. b.i.d.	99.9	1.18	+2.074	+0.285*
Placebo and Diuril, 500 mg. b.i.d.	99.9	1.23	+2.124	+0.334*
Placebo and Hydrodiuril, 25 mg. b.i.d.	99.9	1.47	+2.364	+0.575*
Hydrodiuril, 50 mg., and Diuril, 500 mg. b.i.d.	95	0.52	+1.136	−0.096
Hydrodiuril, 50 mg., and Hydrodiuril, 25 mg.	95	0.28	+0.896	−0.336
Hydrodiuril, 50 mg., and Diuril, 250 mg.	95	0.57	+1.186	−0.046
Diuril, 500 mg., and Diuril, 250 mg. b.i.d.	95	0.05	+0.666	−0.566
Hydrodiuril, 25 mg., and Diuril, 250 mg.	95	0.29	+0.906	−0.326
Diuril, 500 mg., and Hydrodiuril, 25 mg.	95	0.24	+0.856	−0.376

* Significant $P < 0.001$.

Here again, the changes detectable at the end of each week (table 3) were of minimal magnitude and not significant. The analysis of variance on these three parameters did not yield a significant F ratio at the 0.05 level. There were, however, some changes in urine volume and/or 24-hour excretion of sodium and potassium detectable at the end of each week of therapy in individual patients. These individual variations were not of a magnitude to affect the analysis of variance as a whole.

This is particularly interesting in the case of urinary excretion of potassium. Although the serum potassium showed a significant fall at the end of each week of therapy, the urinary excretion of potassium at the same time did not reveal any significant changes.

DISCUSSION

Chlorothiazide (Diuril) and hydrochlorothiazide (Hydrodiuril) are known to be two effective oral diuretics. The mechanism of action of these drugs as diuretic agents has been studied by various investigators.[2-5, 14, 16] In general, they depress the renal tubular reabsorption of sodium, chloride and bicarbonate, and facilitate the secretion of potassium from renal tubules. They produce a marked increase in urine flow and total solute output.

It has also been reported that chronic administration of chlorothiazide is associated with hyperuricemia,[5, 13, 14, 15] but the acute intravenous injection of this drug produces a transient but significant uricosuric response.[11] The observation of the present study indicates that prolonged administration of both agents, chlorothiazide and hydrochlorothiazide, is accompanied by a consistent and highly significant ($P < 0.001$) rise in the serum uric acid concentration. Although the hyperuricemic effect of chlorothiazide has been reported previously, there has been no such report in the case of hydro-

chlorothiazide. The results of the present study suggest that both of these agents cause the elevation of serum uric acid after prolonged oral administration. It was not possible to detect any significant differences between the hyperuricemic effect of chlorothiazide and that of hydrochlorothiazide. The serum uric acid concentration fell to the level of the pretreatment period each time the drug was withheld from the therapeutic regimen, and rose again as soon as the patients resumed medication. Although all of the patients were questioned and examined thoroughly to detect any manifestation of gouty arthritis while the serum uric acid level was high, no such symptoms appeared. It has been reported previously that goutlike symptoms occur only in certain individuals receiving chlorothiazide, and that the intensity of this effect is not necessarily in direct ratio to the height of the serum uric acid level.[13] It can therefore be postulated that gouty arthritis could manifest itself only in those individuals who, for genetic or other reasons, possess a gouty diathesis. The hyperuricemic effect of chlorothiazide and/or hydrochlorothiazide cannot be attributed to an increased catabolism of nucleoproteins or dehydration, since it was not accompanied by serum urea nitrogen elevation.

A possible mechanism of this hyperuricemic action of chlorothiazide has been suggested.[11, 14, 15] The principal mode of renal elimination of chlorothiazide is by glomerular filtration and tubular secretion. This renal tubular transport mechanism for chlorothiazide is thought to be the same as that for para-aminohippurate.[25] It is therefore conceivable that the paradoxic effect of low and high serum levels of chlorothiazide (chronic oral and acute intravenous administration of the drug) upon the serum uric acid concentration is similar to the effect of other uricosuric agents, such as salicylates and probenecid. As has been suggested by Yü and Gutman [26] in the case of salicylates and probenecid, chlorothiazide in low serum concentration (oral administration) probably inhibits the renal tubular secretion of uric acid without altering the renal tubular reabsorption mechanism, and, when it is given intravenously (higher serum concentration), acts as a uricosuric agent by inhibiting the renal tubular reabsorption of uric acid. This hypothesis has been suggested by others, since it has been shown that, upon oral administration, chlorothiazide decreases the renal excretion of uric acid without changing the filtered load of urates.[11]

The saluretic, kaluretic and chloruretic action of chlorothiazide and hydrochlorothiazide has been studied by various investigators.[4, 5, 6, 11, 14, 17, 18, 19] It has been observed that these oral diuretics act as a carbonic anhydrase inhibitor, and have actions similar to those of mercurial diuretics. It has recently been reported that chlorothiazide not only inhibits the reabsorption of the sodium and chloride ions in the proximal renal tubules, but also inhibits the selective reabsorption of the solutes in the distal segment of the renal tubules.[5, 11] Thus the administration of chlorothiazide and hydrochlorothiazide, unlike that of the mercurial diuretics, does not increase

the excretion of free water. Although it has been shown that the administration of chlorothiazide reduces the glomerular filtration rate,[5, 11, 12] Heineman et al. claim that the effects of this drug on free water excretion are "apparently not dependent on changes in the glomerular filtration rate, but result from changes in the tubular reabsorption of solutes and water." [5]

The intravenous administration of chlorothiazide almost always produces a marked increase in urine potassium excretion. The oral administration of these drugs also depresses the renal tubular reabsorption of sodium, chloride and bicarbonate, and thus facilitates the secretion of potassium. This will result in a fall in serum potassium, which is regarded as a potential hazard of prolonged chlorothiazide therapy. In the present study the oral administration of chlorothiazide and hydrochlorothiazide produced a highly significant ($P < 0.001$) fall in serum potassium.

The reduction in serum potassium concentration was not accompanied by any clinical symptoms or signs of hypokalemia, and it was not felt that the patients required potassium supplements during the entire course of the study. Although there are reasons to believe that the patients lost some potassium in the urine at the beginning of each week of therapy, it was not possible to detect any changes in the urinary potassium excretion at the end of each week. As can be seen in table 3, the urinary potassium excretion remained almost unaltered during the placebo therapy period as compared with the drug therapy period. There are three possible explanations for the pattern of urinary excretion of potassium observed in this study:

1. In outpatients, who have varying potassium intakes, the estimation of urinary potassium gives an erroneous impression of potassium balance, as compared with estimation of serum potassium.

2. Perhaps by the end of each week of therapy the patient has once more achieved a state of potassium balance, and the urinary potassium output is similar to that of the pretreatment level.

3. Patients on chlorothiazide may have developed alkalosis which produced a shift of potassium from the extracellular compartment into the intracellular compartment, causing a pattern of low serum potassium level and no change in the 24-hour urinary excretion of this ion.

Although the intravenous administration of chlorothiazide and hydrochlorothiazide produces marked natruresis and chloruresis,[11] the prolonged oral administration of these drugs did not cause a significant change in the serum sodium concentration and the urinary excretion of sodium (table 3). It should be repeated, however, that in all of the patients the serum electrolytes and the concentration of these ions in 24-hour urine specimens were measured in the last 24-hour period of each week of therapy. It has been reported previously that the natruretic effect of chlorothiazide upon continuous oral administration lasts only two to three days, and by the end of the fifth day of drug administration these patients resume normal sodium balance.[16] It may therefore be postulated that all of the patients in this

study were in normal sodium balance at the end of the week, when the serum or the urine was analyzed. On the other hand, there are reasons to believe that these patients had lost some sodium and chloride in the first few days of each period of drug therapy. Loss of weight observed in almost all patients was of statistically significant proportion ($P < 0.01$), and was easily detectable at the end of each week (table 3).

The antihypertensive effect of chlorothiazide and hydrochlorothiazide, when given alone, has been debated by various investigators. Some authors have claimed that these drugs have definite hypotensive action even when taken alone;[22, 23] others have questioned this point, and reported the hypotensive effect of these drugs only in combination with other antihypertensive medications, such as mecamylamine, hydralazine and others.[20, 21] If one takes into consideration the cumulative effect of chlorothiazide during prolonged oral administration, there is little doubt that this agent lowers the blood pressure of hypertensive individuals even when given alone. The patients studied in the present report received no other antihypertensive medication during the entire course of the investigation, and the fall in the systolic and diastolic blood pressure was highly significant ($P < 0.001$). There was no actual difference between the two drugs (chlorothiazide and hydrochlorothiazide) and the two different doses of each drug as far as blood pressure reduction was concerned. The antihypertensive effect of these drugs has been attributed to the natruresis as well as to the reduction in plasma volume which accompanies the administration of these compounds. It has been reported that chlorothiazide administration causes a reduction of 11 to 15% in plasma volume.[16, 24] The fall in blood pressure of hypertensive patients receiving the drug is probably related to reduced plasma volume, since the intravenous infusion of salt-free dextran [16] will abolish the antihypertensive effect of chlorothiazide.

Summary

1. A "double-blind" study comparing the diuretic and hypotensive effect of chlorothiazide and hydrochlorothiazide is reported.

2. There was a highly significant ($P < 0.001$) reduction in the systolic and diastolic blood pressures of 23 hypertensive patients put on prolonged oral chlorothiazide and hydrochlorothiazide therapy alone. There was no significant difference between the two drugs and two different doses of each drug on systolic and diastolic blood pressures of hypertensive patients.

3. Chlorothiazide and hydrochlorothiazide in two different doses cause significant losses of total body weight ($P < 0.001$). The effect of two different doses of each drug on total body weight was not significantly different.

4. Hydrochlorothiazide at the dose level of 100 mg. per day caused a more significant fall in serum potassium concentration ($P < 0.001$) than did chlorothiazide at the dose level of 1000 mg. per day ($P < 0.01$). The

smaller dosage administration of hydrochlorothiazide (50 mg. per day) also produced a significant fall in serum potassium level ($P < 0.05$), while the smaller dosage of chlorothiazide did not ($P > 0.05$).

5. Prolonged oral administration of both chlorothiazide and hydrochlorothiazide caused hyperuricemia to an identical degree.

6. The changes in the mean serum sodium concentration, 24-hour urinary excretion of sodium and potassium and the urine volume, when measured at the end of each week of therapy, were not significant after chlorothiazide and hydrochlorothiazide when compared with placebo.

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SUMMARIO IN INTERLINGUA

Esseva interprendite un bis-occulte essayo clinic pro comparar le action saluretic, hypotensive, e hyperuricemic de chlorothiazido con illo de hydrochlorothiazido—ambes in duo differente doses diurne: 1.000 e 500 mg de chlorothiazido e 100 e 50 mg de hydrochlorothiazido.

Methodos: Con le uso de un complete aleatoriisation, le essayo clinic esseva organisate secundo un leve modification del classic quadrato latin. Vinti-tres patientes con chronic hypertensive morbo cardiovascular esseva includite in iste studio. Le concentration de natrium, de kalium, e de acido uric in le sero e lor excretion in le urina de 24 horas esseva mesurate regularmente. Le effectos del administration oral del droga e del placebo super le tension de sanguine e le total peso corporee esseva etiam observate. Pro le analyse del datos le classic methodo del "analyse bidirectional de variantia" esseva usate. Pro determinar le signification del assi obtenite ration "F" e pro effectuar omne le pertinente comparationes inter le valores medie, un analyse additional esseva effectuate secundo le methodo describite per Scheffé.

Resultatos: Ben que il occurreva in omne le patientes studiate un significativissime reduction del tension sanguinee systolic e etiam diastolic ($P < 0{,}001$), il non existeva un significative differentia inter le duo drogas o inter le duo doses del mesme droga.

Le prolongate administration oral del un e del altere del duo dosages de chlorothiazido e de hydrochlorothiazido causava un altemente significative augmento del concentration seral de acido uric ($P < 0{,}001$). Le valores medie del nitrogeno de urea in le sero remaneva intra le limites del norma durante le periodo del studio. In despecto del nivellos normal de nitrogeno de urea in le sero in omne le patientes, le nivello medie del acido uric in le sero esseva elevate mesmo ante le administration de chlorothiazido o de hydrochlorothiazido esseva comenciate. Le signification de iste observation como un indication possibile de un precoce deterioration renal in hypertension es currentemente sub investigation.

Le differentia del concentration medie de kalium seral inter le administration de chlorothiazido, hydrochlorothiazido, e placebo in le gruppo total de patientes esseva altemente significative ($P < 0{,}0001$). Le reduction del kalium seral esseva plus marcate con le doses plus forte del duo drogas. Le comparation del doses plus basse

del drogas monstrava que le reduction del kalium del sero esseva plus marcate in le caso de hydrochlorothiazido que in le caso de chlorothiazido.

Le alterationes del concentration seral de natrium non esseva significative. Isto esseva attribuite al facto que le patientes reteneva un normal balancia de natrium al tempore quando le natrium del sero esseva mesurate. Le variationes del volumine de urina in 24 horas e del excretion urinari de natrium e kalium in 24 horas non esseva de un magnitude que poteva afficer le analyse de variantia in su totalitate.

Chlorothiazido e hydrochlorothiazido exerce—a differente nivellos de dosage—le mesme effectos super le tension sanguinee e super le nivello seral de natrium, de kalium, e de acido uric. In le practica general le doses plus basse debe esser recommendate, proque illos ha le mesme effecto hypotensive como le doses plus forte, durante que lor effecto kaliuretic es minus marcate.

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CHROMOSOME ABNORMALITIES IN CERTAIN DISEASES OF MAN *

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Chromosomes, as the carriers of the genes which transmit hereditary characteristics, have always excited attention among biologists. In the late nineteenth century it became clear that each species had a constant number of chromosomes, and that this number was invariable within the species. Attempts were made to determine the chromosome number in man by Hansemann as early as 1891,[1] but no convincing answer to this problem came until 1912, when de Winiwarter reported 47 chromosomes in spermatogonial metaphases.[2] This continued to be controversial until about 1921, when Painter [3] appeared to settle all doubts by demonstrating an additional small chromosome, the Y chromosome, in primary spermatocytes. It was concluded that man had 48 chromosomes. This conclusion remained virtually unchallenged until 1956, when Tjio and Levan,[4] using cell culture methods, announced that 46 and not 48 was the correct diploid number in man. This new result was soon confirmed by Ford and Hamerton [5] and others in Britain, and by Chu and Giles [6] and Tjio and Puck [7] in the United States. Cytologic technics have continued to improve, and a reasonably accurate analysis of the normal human chromosome constitution has now been obtained.

Human chromosomes have proved to be difficult to examine directly, and for this reason have been rather neglected by cytogeneticists. However, plants and lower organisms with low chromosome numbers have been studied extensively, and none more so than Drosophila. Over 40 years ago the classic work of Calvin Bridges [8, 9] on Drosophila demonstrated that some flies with exceptional characteristics had abnormal chromosome numbers. His Drosophila breeding experiments were a perfect proof of the chromosome theory of heredity, and incidentally suggested a new etiologic mechanism in congenital disease. He further showed that these abnormal chromosome numbers were produced by *nondisjunction* of the chromosomes during meiosis in the parental germ cells. The fact that some of these flies were types of intersex led Painter [10] in 1923 to suggest that hermaphroditism in man might have a similar origin. However, no progress was made in this

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direction until last year when, within a very short time, abnormal chromosome numbers were found in several human disorders, including mongolism.

Calvin Bridges' work on nondisjunction in Drosophila now became of greater theoretic importance in medicine, because it appears that this is the mechanism most likely to explain abnormal chromosome numbers in man. One hesitates to apply directly to man the conclusions obtained in experiments on Drosophila, but the findings in these human chromosome anomalies parallel in such a striking way Bridges' results that his work deserves close consideration. For example, increased maternal age increases the frequency of nondisjunction in Drosophila. Increased maternal age is also a well-known characteristic of mongolism. Other factors which increase the frequency of nondisjunction in these flies are irradiation, and exposure to atmospheres containing a high content of carbon dioxide.[11]

Before nondisjunctional chromosome anomalies in man are considered, it seems appropriate to make brief mention of the cytologic methods used in human chromosome analysis.

Human Chromosome Analysis

Present methods of human chromosome analysis depend largely upon cell cultures exposed to minute doses of colchicine, which arrests and so accumulates cells in a suitable stage of mitosis. Squash preparations are made after the cells have been exposed to a hypotonic solution which causes the cells to swell and so disperses the chromosomes. We favor a modification of the short-term bone marrow culture method of Ford and his colleagues.[12, 13]

Chromosomes at the metaphase stage of mitosis appear as rod-shaped structures, split longitudinally into two chromatids which lie side by side and are attached to one another at a fixed point, the kinetochore or centromere. The individual chromosomes vary both in length and in the position of the kinetochore, which may be median, submedian or subterminal. Of the 46 chromosomes, there are 22 pairs of nonsex chromosomes or autosomes, and two sex chromosomes paired in the female (XX) and unpaired in the male (XY). Measurements of the chromosomes can be made from enlarged photomicrographs or camera lucida drawings. Comparison of the total length to the long arm/short arm index allows accurate identification of the majority of the chromosome pairs. The Y chromosome can usually be identified as the largest chromosome in a group of the five smallest chromosomes. As there are only four chromosomes in this group (Group VII) in the female, it is possible to determine the sex chromosome constitution by arranging the chromosomes into seven groups.[13] The X chromosome is difficult to identify with complete certainty, but it appears to be the seventh largest chromosome, and is included in Group III. Two pairs of chromosomes, No. 14 and No. 21, bear "satellite bodies" on their short arms, and this additional feature helps in their identification.

Mongolism: The first indication of nondisjunction in man was the dis-

covery of an extra chromosome in mongolism. This was reported in January, 1959, by Lejeune and his collaborators [14] in Paris, and has been confirmed since then by numerous investigators.[15, 16, 17] The additional chromosome is one of the small chromosomes, No. 21, which frequently bears satellited bodies. There are thus three instead of two identical chromosomes corresponding to No. 21 (figure 1). It is possible that the duplication of the genes carried on this extra chromosome by disturbing the normal genetic balance is responsible for the mental defect and associated anomalies of mongolism. Nondisjunction of chromosome No. 21 during meiosis in

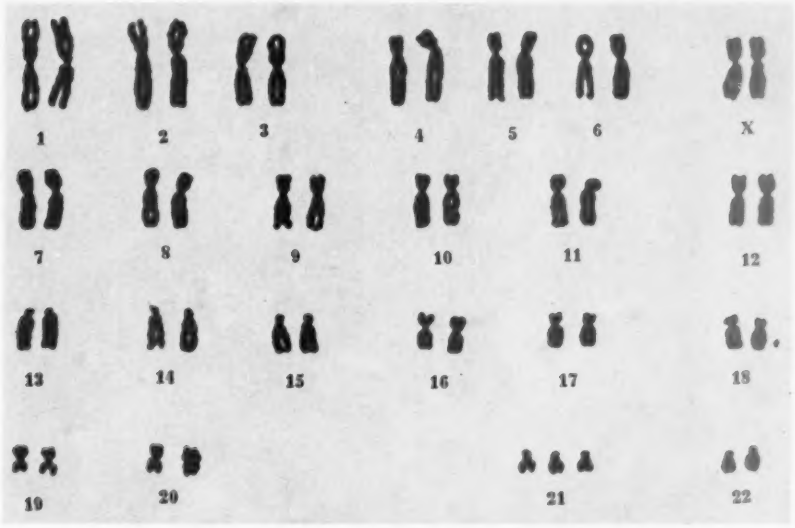

FIG. 1. Karyotype of a female mongoloid idiot.

one or other of the parent's germ cells, or possibly during the early division of the zygote, is the best explanation so far presented. The concordance in monozygotic Mongol twins suggests that the nondisjunction occurs during meiosis in the parental germ cells, and is not mitotic. The high maternal age suggests, in addition, that the fault arises in oögenesis and not in spermatogenesis. The frequency of occurrence of mongolism, which is about one in 600 to 700 of the general population,[18] indicates that nondisjunction cannot be considered to be a rare phenomenon in man.

The reported increased frequency of leukemia among Mongols [19] suggests the possibility that the abnormal basic chromosome number in mongolism is a predisposing factor. Because of the technical difficulty in separating counts in leukemic cells from counts in normal marrow cells, it is not yet clear whether the leukemic process in man is associated with chromosome abnormalities. One case of acute leukemia has been described

TABLE 1

Human Sex Anomalies

		Nuclear Sex	Chromosome Constitution	Gonads	Sex Differentiation		
					External Genitalia	Genital Ducts	Secondary Sex Development
True hermaphroditism	(a) Chromatin-positive	+ve	46 (XX)	Testis or ovotestis *and* Ovary or ovotestis	Ambiguous	♂ & ♀	M or F
	(b) Chromatin-negative	−ve	?46 (XY)		Ambiguous	♂ & ♀	M or F
Male pseudohermaphroditism	(a) Testicular Feminization	−ve	46 (XY)	Testis	♀	Usually only ♂	F
	(b) With Ambiguous Differentiation	−ve	46 (XY)	Testis	Ambiguous	♂ or ♀	M or F
Female pseudohermaphroditism	(a) Congenital Adrenal Hyperplasia	+ve	46 (XX)	Ovary	♂	♀	F
	(b) Maternal Androgens, etc.	+ve	?46 (XX)	Ovary	♂	♀	F
Gonadal aplasia (Turner's syndrome, etc.)	(a) Chromatin-negative	−ve	45 (XO)	Ovarian streak	♀	♀	F
	(b) Chromatin-positive	+ve	46 (XX) or 45 (XO)	Ovarian streak	♀	♀	F
Primary microörchidism (Klinefelter's syndrome)	(a) Chromatin-positive	+ve	47 (XXY)	Testis	♂	♂	M
	(b) Chromatin-negative	−ve	46 (XY)	Testis	♂	♂	M
Primary amentia and microörchidism with triple-X/Y		Double positive	48(XXXY)	Testis	♂	♂	M
Ovarian dysgenesis with triple-X		Double positive	47 (XXX)	Ovary	♀	♀	F

as having a modal chromosome number of 48 in addition to showing structural abnormalities.[20] We have so far examined four untreated cases of acute and two of chronic leukemia. The modal diploid number was normal in each, although the proportion of hyperploid cells was much higher than is usually found in normal bone marrow.[21]

The Sex Anomalies: The second group of chromosome anomalies in man to be considered is that in which nondisjunction involves the sex chromosomes. We now know of at least four different types of sex anomaly associated with abnormal complements. Table 1 lists the conditions in which abnormal sex differentiation is found. We have been particularly

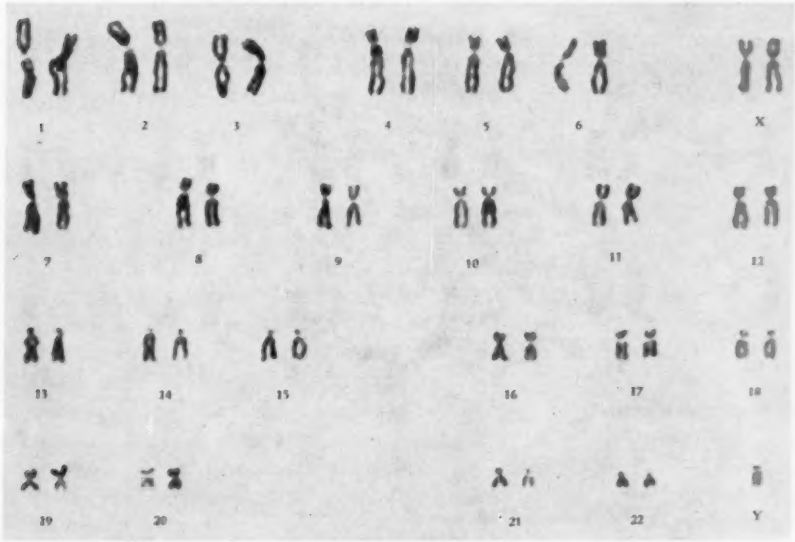

FIG. 2. Karyotype of a patient with chromatin-positive Klinefelter's syndrome.

interested in making chromosome studies in these disorders in an effort to learn more about the specific role of the sex chromosomes in sex determination, and also to obtain evidence on the origin of the sex chromatin body. Since the discovery of a sex difference in intermitotic mammalian nuclei by Barr and Bertram in 1949,[22] nuclear sexing has played a very important part in the detection, diagnosis and understanding of human intersexuality.

The discrepancy between the nuclear sex finding and the somatic appearance in chromatin-positive Klinefelter's syndrome and in chromatin-negative gonadal aplasia (Turner's syndrome) prompted the investigation of the sex chromosome constitution in these cases, and led to the discovery of two more abnormalities in chromosome number. Jacobs and Strong [23] and Ford and his colleagues [24] were the first to show that patients with chromatin-

positive Klinefelter's syndrome have 47 chromosomes, and that the extra chromosome is one of the sex chromosomes, giving these individuals a sex chromosome complement of XXY (figure 2). Cases of chromatin-negative Turner's syndrome have 45 chromosomes, and Ford et al.[25] and others have demonstrated that it is one of the sex chromosomes which is missing, giving an XO sex chromosome complement (figure 3).

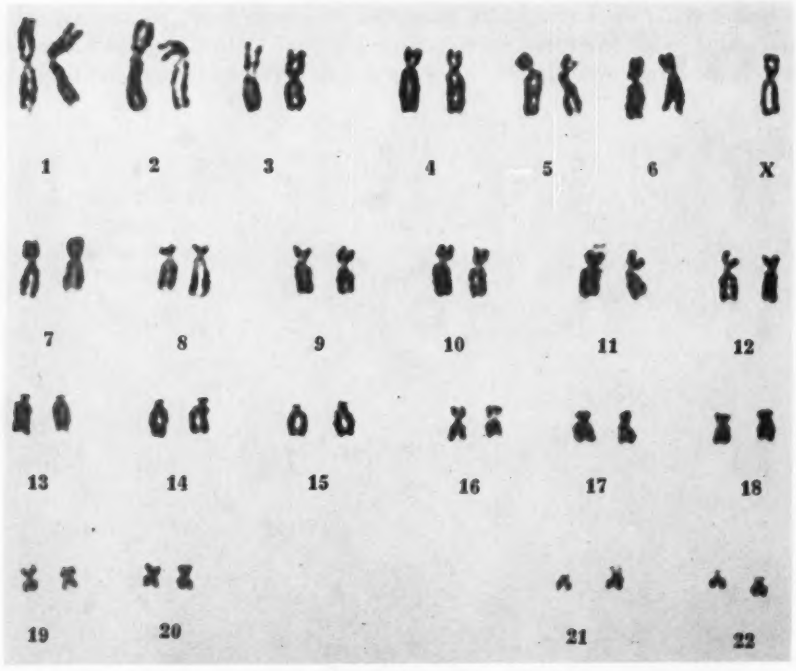

FIG. 3. Karyotype of a patient with chromatin-negative Turner's syndrome.

We have been fortunate in having two true hermaphrodites available for chromosome analysis.[13] One case has a testis and male genital ducts on one side, and had a uterus, tube and ovary on the other side. Our second case had an ovotestis on one side and a rudimentary fallopian tube and ovary on the other. The basic chromosome number in each is 46, with an XX sex chromosome constitution. In one, a high proportion of cells had 47 chromosomes, the analysis being consistent with an XXX sex chromosome complement. In none of the preparations from these two cases was there any evidence of a Y chromosome. The recently reported studies in two other true hermaphrodites [26, 27] also show an XX pattern. So far, this is the only type of sex anomaly reported in which male sex differentiation has occurred in the absence of a Y chromosome.

This observation is of importance in view of the recent theories on sex determination in man. The demonstration of an XXY sex chromosome constitution associated with male sex differentiation in chromatin-positive Klinefelter's syndrome, and the XO pattern and female sex differentiation in chromatin-negative gonadal aplasia, suggests that, in man, the Y chromosome is strongly male-determining. This is not the case in Drosophila, where the XXY is a fertile female and the XO is a sterile male, sex determination apparently being a balance between masculinizing genes on the autosomes and feminizing genes on the sex chromosomes, the Y playing no significant part in the system. The findings in true hermaphroditism in man suggest that the normal Y chromosome is not the only important factor to be considered in the initiation of male differentiation.

In neither male nor female pseudohermaphroditism is there evidence of chromosomal nondisjunction, for the normal chromosome number is found, and the sex chromosome constitution corresponds to the type of gonad.[28, 29] The only possible exception is to be found in the group of male pseudohermaphrodites who have very ambiguous sex differentiation. Here the clinical and pathologic findings suggest varying types of differentiation between chromatin-negative gonadal aplasia and chromatin-negative true hermaphroditism. One particular case that we have studied concerns a child reared as a male who was found to have a uterus and tubes with a testis on one side and a gonadal streak on the other. The chromosome findings were interpreted as showing a diploid number of 45 and an XO chromosome constitution. Here again, it appears that differentiation of a testis has occurred in the absence of a Y chromosome.

Chromatin-positive Klinefelter's syndrome is by far the most frequent of the sex anomalies in man, and appears to be only a little less common than mongolism. A recent estimate is one in 400 of all male births.[30] It occurs in over 1% of institutionalized mentally defective males,[31] and in about 3% of all subfertile patients attending a male infertility clinic.[32] As in mongolism, there appears to be a maternal age effect pointing to nondisjunction during oögenesis rather than spermatogenesis.[33] Evidence in support of meiotic nondisjunction in the mother comes from a study of the inheritance of color blindness in the families of Klinefelter cases. Nowakowski and his collaborators [34] report three color-blind cases of chromatin-positive Klinefelter's syndrome. As the mutant gene transmitting red-green color blindness is carried as a recessive characteristic on the X chromosome, the chromatin-positive Klinefelter patient must be homozygous to show the defect. The parents of two of Nowakowski's cases were found to have normal color vision; and the mother, but not the father, of the third patient was color blind. The inheritance of color blindness by the patient with the color-blind mother is readily explained by nondisjunction of the X chromosomes during either the first or the second meiotic division during oögenesis in the mother, leading to an abnormal ovum containing two X chromosomes,

each of which carries the mutant gene for color blindness. This abnormal XX ovum is fertilized by a normal Y-bearing sperm (figure 4). In the other two cases, as both parents had normal color vision, the mother must have been a carrier, and meiotic nondisjunction could have occurred only at the second (equational) meiotic division. An alternative explanation involves crossing over.

In chromatin-negative gonadal aplasia, meiotic nondisjunction during spermatogenesis in the father, or mitotic nondisjunction during the first cleavage division, is suggested by color vision studies and supported by the absence of a maternal age effect.[35] For example, four color-blind cases

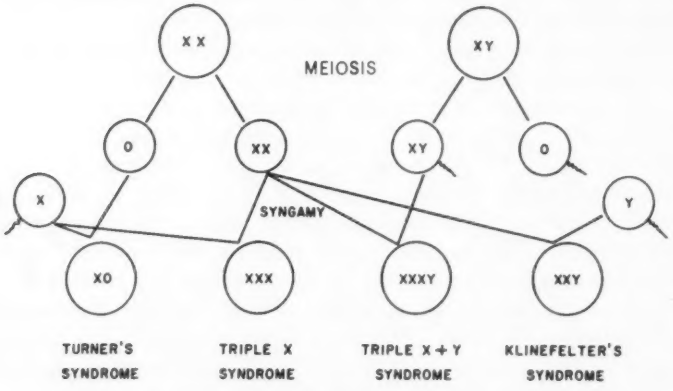

FIG. 4. Diagram illustrating primary meiotic nondisjunction.

are cited by Ford et al.,[25] all of whom had parents with normal color vision. If each of these individuals was the product of a zero ovum (carrying no sex chromosome) and an X sperm, the father would be color blind. As this was not the case, it must be concluded that the mothers, who also had normal color vision, were heterozygous carriers of the mutant gene, and that zero sperm were produced by meiotic nondisjunction occurring during spermatogenesis.

The last two varieties of sex anomaly to be considered are the XXX chromosome anomaly,[36] analogous to the "super female" of Drosophila, and the XXXY chromosome anomaly,[37] which appears clinically to be a variant of Klinefelter's syndrome. Jacobs' triple X case was a clinically unremarkable female who had secondary amenorrhea. Our two XXXY cases with a diploid number of 48 are mentally defective males with testicular atrophy (figure 5). A very interesting nuclear sex finding which led to their detection is present in these two conditions. A large proportion of nuclei contain two sex chromatin masses, instead of the usual one. As this finding is associated with three and not four X chromosomes, it follows that the sex chromatin body may represent heterochromatic material from

a single X chromosome and not, as was at first suggested, heterochromatic areas from two X chromosomes showing somatic pairing.[38] This implies a difference in chemical properties and behavior between the two X chromosomes in the normal female. It is possible that the differentiation is produced by paternal transmission and lost during oögenesis. The findings in the triple X individuals would appear to confirm in man the report by Ohno et al.[39] that, in the rat, a sex chromatin body is formed by a single X chromosome which exhibits positive heteropyknosis at prophase. It is of interest that, in the chicken, a sex chromatin mass is also present in the female,[40] and as this is the heterogametic sex, it could only be derived from one sex chromosome.

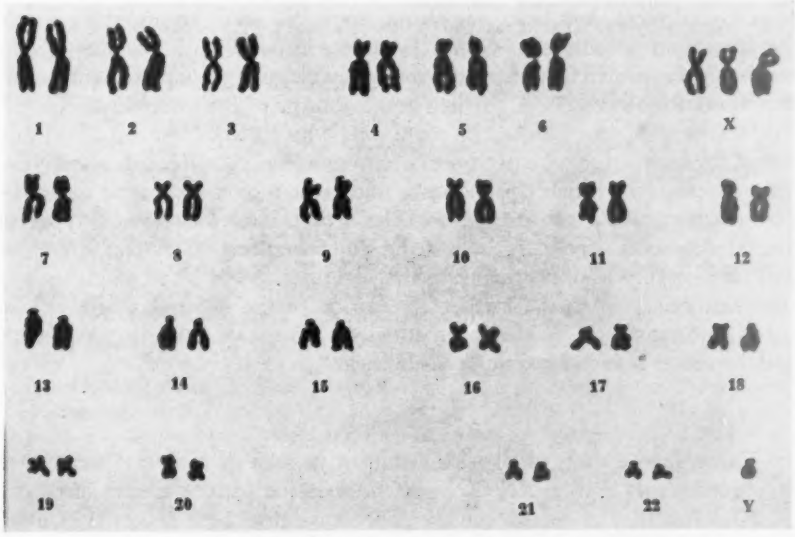

FIG. 5. Karyotype of a patient with the triple-X/Y syndrome.

Meiotic nondisjunction occurring during oögenesis, resulting in XX ova which are fertilized by normal X-bearing sperm, is a possible explanation for the XXX individual. However, mitotic nondisjunction at the first cleavage division, with loss of the hypoploid daughter cell, is as good an alternative.

It is rather more difficult to postulate a mechanism for the XXXY individual. Experience with Drosophila is not informative, because this type is apparently unknown, although theoretically, mating the fertile XXY female fly with the XYY male could produce such offspring by secondary nondisjunction. We have excluded secondary nondisjunction in our XXXY cases only insofar as the mothers have been shown to have a single complement of sex chromatin and presumably have only two X chromosomes. It is hoped that the chromosomes in the parents of these cases may be ex-

amined; until these results are available, it seems inappropriate to discuss secondary nondisjunction further. Other alternative mechanisms involve primary meiotic nondisjunction or mitotic nondisjunction. It is unfortunate that none of these hypotheses can be tested until some method of marking the X chromosomes becomes available.

An account of human chromosome anomalies would be incomplete without mentioning the remarkable case of Ford et al.,[41] who combined the clinical features of Klinefelter's syndrome and mongolism, and was found to have 48 chromosomes, an XXY sex chromosome complement, and an additional chromosome No. 21. Turpin et al. report [42] another chromosome anomaly in a boy aged four and one-half years who had multiple congenital anomalies of the spine. He has 45 chromosomes with an XY sex chromosome complement, and lacks one chromosome No. 22. In addition, one of the larger chromosomes in Group IV is remarkable in that it has a very much larger short arm than does its homologue. It appears that this chromosome has been involved in a translocation with chromosome No. 22.

Despite the large number of conditions which have been examined and found to show an apparently normal chromosome constitution, many conditions remain in which chromosome studies may be as revealing as in the case of mongolism. Investigation of abortions and the various types of mental deficiency is clearly indicated. Improvements in cytologic technic will undoubtedly lead eventually to the identification of small deletions and translocations, and to the further elucidation of the dissimilar behavior of the X chromosomes. Chromosome analysis in man is still in its infancy, and the future is full of exciting possibilities.

Summary

The events leading to the establishment in man of a diploid number of 46 chromosomes and an XX/XY sex chromosome pattern are reviewed.

Abnormalities in chromosome number have now been reported in mongolism and in some of the sex anomalies, particularly chromatin-positive Klinefelter's syndrome and chromatin-negative Turner's syndrome. Two male patients with an XXXY constitution are also discussed. The findings in leukemia are reviewed.

Nondisjunction is suggested as the mechanism by which these abnormalities are produced.

Summario in Interlingua

Es revistate le evenimentos que resultava in le establimento del correcte numero diploidic de 46 chromosomas in le homine. Iste successo dependeva del disveloppamento de nove technicas cytologic. Le autores ha adoptate un modificate version del rapide methodo de culturation de medulla ossee secundo Ford.

In 1959, le prime anormalitate chromosomal in humanos esseva reportate per Lejeune e su gruppo pro mongolismo. Le presentia de un chromosoma 21 supernumerari ha essite confirmate per plure gruppos. Le augmentate incidentia de

leucemia inter mongoloides suggere le possibilitate que le aneuploidia predispone al disveloppamento de ille morbo. Un caso de leucemia ha essite reportate con un numero modal de 48, sed in omne nostre sex casos, le sol anormalitate esseva un proportion plus que normal de cellulas hyperploide.

Depost le discoperta de Barr del massa de chromatina de sexo in femininas normal, su absentia in le majoritate del casos de syndrome de Turner e su presentia in multe casos de syndrome de Klinefelter ha stimulate un grande interesse. Ford e su collaboratores ha monstrate que patientes con syndrome de Turner a negativitate chromatinic (aplasia gonadal) ha 45 chromosomas con le absentia de un chromosoma de sexo. Del altere latere, in syndrome de Klinefelter a positivitate chromatinic, il existe un chromosoma supernumerari con le configuration XXY. Iste observationes suggere que le chromosoma Y es un forte determinante mascule. Tamen, il es possibile que isto non es completemente correcte, proque le duo casos del autores de hermaphroditismo ver ha basicamente 46 chromosomas con un configuration XX.

In pseudohermaphroditismo mascule e feminin, nulle anormalitate del chromosomas pote esser detegite, e le constitution sexual corresponde al typo gonadal.

Finalmente, le syndromes associate con duple corpores de chromatina de sexo es considerate. Jacobs e su collegas ha reportate le caso de un patiente con amenorrhea secundari e un numero de chromosomas de 47 con un configuration XXX del chromosomas de sexo. Nostre duo patientes, qui es mentalmente defective masculos con atrophia testicular, ha 48 chromosomas e un configuration XXXY.

Nos ha confirmate omne le supra-mentionate constatationes con le exception del situation in pseudohermaphroditismo feminin.

Inter iste syndromes, illo de Klinefelter a positivitate chromatinic es le plus frequente. Su incidentia es circa 1 in 400 natos mascule.

Como Bridges lo ha monstrate pro Drosophila, il es opinate que nondisjunction es etiam responsabile in le homine pro le deviationes del numero de chromosomas. Tanto in mongolismo como in syndrome de Klinefelter il ha un defecto per le etate avantiate del matre. Iste facto, insimul con le arbores genealogic de achromatopsia reportate per Nowakowski, suggere que le nondisjunction occurre in le matre. In syndrome de Turner, le disponibile datos indica que le error se trova plus tosto in le spermatogenese.

Es etiam opinate que nondisjunction representa le explication del syndrome de XXX, sed isto debe occurrer a duo divisiones cellular pro render comprehensible le zygote XXXY.

Es etiam revistate le occurrentia de syndrome de Klinefelter e mongolismo in un sol patiente e le reporto de un translocation de parte de numero 22 a un grande chromosoma telocentric (13–15) in un patiente con congenite anormalitates del spina dorsal.

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CARBOHYDRATE METABOLISM IN PENTOSURIA*

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Pentosuria, or chronic essential pentosuria, is one of four hereditary disturbances which Garrod [1] over 50 years ago classified as inborn errors of metabolism. It is an innocuous condition, presumably present from birth, and has been described almost exclusively in Jews. The characteristic urinary excretion of a relatively constant amount of L-xylulose, varying from 1 to 4 gm. per 24 hours,[2] unrelated to dietary factors, distinguishes hereditary pentosuria from several other situations in which milligram quantities of certain 5-carbon sugars other than L-xylulose are found in the urine. These include alimentary pentosuria, in which arabinose or xylose may be excreted following the ingestion of unusually large quantities of certain fruits, including plums, cherries and grapes. In addition, small amounts of D-ribose are often present in urine from healthy subjects, and slightly larger quantities may be found in the urine of some patients with muscular dystrophy, presumably as a result of the excessive breakdown of ribose-containing coenzymes in degenerating muscle.[3] Finally, traces of ribulose have been found in the urine of normal individuals.[4]

During the last decade, information has been accumulated which points to the operation of the glucuronic acid oxidation pathway in normal human subjects and to a genetically-determined block in this pathway in individuals with pentosuria. It is the purpose of this paper to review this information and to consider the probable site of the enzymatic defect in pentosuria.

Carbohydrate Metabolism in Normal Individuals

It is now generally accepted that most of the glucose metabolized by the mammalian organism traverses the Embden-Meyerhof-Parnas, or glycolytic, pathway. (For a detailed description of the reactions involved, see reference 5.) This series of reactions results in the conversion of a molecule of glucose to two molecules of pyruvic acid. The pyruvic acid may then be further metabolized to carbon dioxide by way of the tricarboxylic acid cycle. The complete oxidation of one molecule of glucose by way of the glycolytic and tricarboxylic acid cycle reactions results in the synthesis of as many as 32 molecules of the high energy phosphate compound, adenosine triphos-

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phate. Since a chief function of carbohydrate oxidation is to provide the organism with utilizable energy, it is not surprising that this mechanism accounts for the bulk of the glucose utilized. Indeed, skeletal muscle, the tissue in which most glucose is metabolized, contains large quantities of the enzymes involved in the glycolytic and tricarboxylic acid schemes, but almost none of the enzymes involved in other pathways of carbohydrate metabolism. Although the pentose phosphate pathway (hexose monophosphate shunt) [6] participates in glucose metabolism to a much smaller extent than does the glycolytic, it is equally essential for the normal function of body cells. The pentose phosphate scheme not only affords a mechanism for the production of ribose, the essential carbohydrate component of ribonucleic acid and of

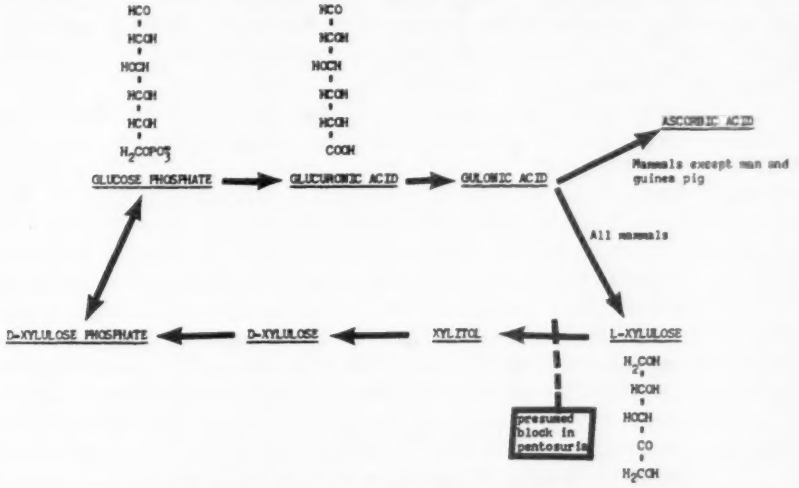

FIG. 1. The glucuronic acid oxidation pathway. (For a more detailed account of the reactions involved, see reference 5.)

several coenzymes, but also represents the principal mechanism for the conversion of triphosphopyridine nucleotide to its reduced form. Reduced triphosphopyridine nucleotide is a co-factor in a variety of reductive synthetic reactions, including several leading to the production of such essential cellular components as cholesterol, fatty acids, steroids, and certain amino acids. Thus, one may reasonably assume that both the glycolytic and the pentose phosphate pathways of carbohydrate metabolism are required for the survival of the organism. Such does not appear to be the case for the recently described glucuronic acid oxidation route (figure 1), at least in man. In most animal species this pathway affords a means of ascorbic acid biosynthesis, but in man and the guinea pig, ascorbic acid cannot be synthesized and must be provided in the diet. An early reaction, described in figure 1, results in the reduction of glucuronic acid to gulonic acid. Most animal

species are able to convert products of gulonic acid either to ascorbic acid or to L-xylulose. In man and the guinea pig, however, only the latter compound is produced, because one of the enzymes which mediate the conversion of gulonic acid to ascorbic acid is absent. The carbon atom oxidatively removed (as carbon dioxide) in the gulonic acid to L-xylulose steps corresponds to the sixth carbon atom of the parent glucose molecule, and hence this pathway has also been called the C-6 oxidation pathway. In the subsequent reactions, shown in figure 1, L-xylulose may be converted to D-xylulose phosphate, which is an intermediate in the pentose phosphate pathway, and which may be converted to hexose phosphate. Thus, this scheme of metabolism provides a mechanism for the conservation of the carbon of glucuronic acid, which might otherwise be excreted. That it is not an essential scheme in the economy of the human organism is suggested by the innocuous nature of pentosuria, the condition in which this pathway is presumably blocked.

The elucidation of the reactions involved in the glucuronic acid oxidation pathway has provided insight not only into the origin of the L-xylulose occasionally found in trace amount in normal urine, but also into the probable site of the defect in individuals with pentosuria. An explanation is now also available for the hitherto poorly understood increase in L-xylulose excretion by pentosuric subjects given glucuronic acid. Such an increase was first noted by Enklewitz and Lasker,[2] who also observed a stimulation of pentose excretion following the intake of such drugs as borneol, antipyrine and menthol. Aminopyrine ingestion had previously been noted to cause an increase in pentose excretion by individuals with pentosuria,[7] and Enklewitz and Lasker ascribed the effect of the drugs to their glucuronogenic action. The mechanism of drug action is still not understood, but the demonstration that glucuronic acid is a precursor of L-xylulose provides a ready explanation for the stimulation of pentose excretion following glucuronic acid administration.

The Defect in Pentosuria

Much of our understanding of the biochemical lesion in pentosuria we owe to the studies of Touster and his associates.[8-11] These investigators confirmed the observation of Enklewitz and Lasker that the ingestion of glucuronolactone by pentosurics is followed by an increased excretion of xylulose, and then demonstrated that the conversion of glucuronolactone to xylulose in such individuals is a direct one. They found that pentosuric individuals can metabolize the sixth but not the first carbon atom of glucuronolactone. Touster also demonstrated that normal human subjects and guinea pigs may excrete traces of L-xylulose, and that this excretion is slightly augmented following glucuronolactone ingestion. These latter observations strengthen the concept that L-xylulose is a metabolic intermediate in normal subjects.

During recent years the results of three series of studies carried out in

our laboratory have provided further evidence for the function of the glucuronic acid oxidation pathway in normal individuals, and for an impairment in this pathway in subjects with pentosuria. These experiments will be briefly summarized.

1. Conversion of Glucuronolactone Carbon to Carbon Dioxide [12]: As has been noted, available evidence suggests that normal subjects can metabolize glucuronic acid completely, and that pentosuric individuals are capable of metabolizing the sixth carbon atom of the glucuronic acid molecule, but excrete the remaining five-carbon fraction as pentose. Then, following the administration of glucuronolactone uniformly labeled with radioactive carbon, there should be six times as much isotope in the expired carbon

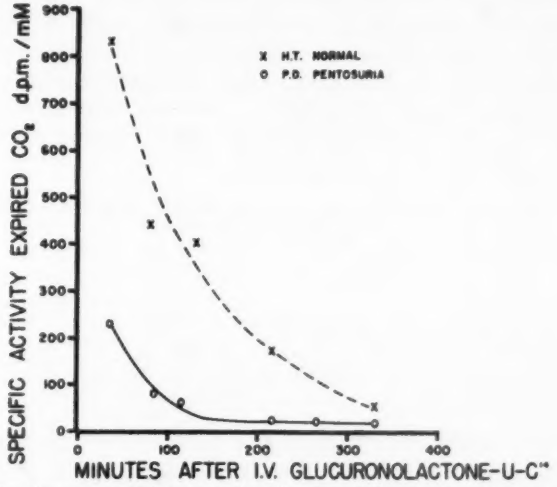

FIG. 2. Respiratory excretion of radioactive CO_2 following the intravenous administration of 5 microcuries of glucuronolactone uniformly labeled with C^{14} to a normal subject and to a pentosuric.

dioxide of a normal individual as is present in that of a pentosuric. Such proved to be the case in a study, the results of which are shown in figure 2. In this experiment 5 microcuries of glucuronolactone uniformly labeled with C^{14} (obtained through the courtesy of Dr. N. Artz, Corn Products Refining Company, Argo, Illinois) were given intravenously to a pentosuric subject and to an individual with no abnormality of carbohydrate metabolism. Samples of expired air were collected at intervals for six hours thereafter and were analyzed for carbon dioxide and for radioactivity. In this period of time, 16% of the administered C^{14} appeared in the expired air of the normal subject, and 2.6% in that of the pentosuric, almost exactly the six-fold difference predicted.

2. Conversion of Glucuronolactone Carbon to Urinary Ribose [13]: The study of glucuronolactone carbon conversion to carbon dioxide strongly

supports the view that glucuronic acid metabolism is impaired in pentosuria. Some information concerning the site of the defect may be deduced from the results of a second isotopic experiment. In this study we used a technic for trapping ribose suggested by the observation of Tabor and Hayaishi [14] that after imidazoleacetic acid (ImAA) is administered to animals, some ImAA conjugated with ribose (ImAA riboside) is excreted in the urine. We had previously found that this compound is not toxic in man, and that, following its administration, substantial quantities of ribose can be conveniently isolated from the urine. With this technic we were able to demonstrate ribose synthesis from hexose in normal individuals by way of the oxidative and the nonoxidative reactions of the pentose phosphate pathway.[15] If the glucuronic acid oxidation pathway were operative, it would provide a mechanism for the conversion of glucuronolactone carbon to ribose in the following fashion: glucuronolactone → L-xylulose → D-xylulose → D-xylulose 5-phosphate → D-ribose 5-phosphate. Thus, the simultaneous administration of imidazoleacetic acid and of glucuronolactone uniformly labeled with C^{14} would be followed by the excretion of ImAA riboside containing C^{14}-

TABLE 1

Urine L-Xylulose and Ribose after Administration of Imidazoleacetic Acid (ImAA) and Glucuronolactone-C^{14}

Subject	L-Xylulose		ImAA Riboside Ribose	
	Micromoles	Counts per Minute	Micromoles	Counts per Minute
Control	0.5	300	140	4,600
Pentosuric	3,950	336,000	208	190

labeled ribose. On the other hand, if this pathway were blocked in pentosuria at a site beyond L-xylulose, then a pentosuric might be expected to excrete radioactive xylulose, but nonisotopic ribose. (Since there is no reason to postulate an impairment in the pentose phosphate pathway in pentosuria, the synthesis of riboside ribose from endogenous glucose should proceed normally.) The results of such an experiment are summarized in table 1. The significant C^{14} incorporation in the urinary ribose of the normal subject is consistent with the conversion of glucuronolactone to ribose by way of the reactions of the glucuronic acid oxidation and the pentose phosphate pathways. The pentosuric subject excreted ribose in an amount comparable to that excreted by the normal individual, but the virtual absence of radioactivity indicates that it was derived from sources other than glucuronolactone. The large quantity of isotope in the urinary L-xylulose is in agreement with Touster's demonstration that glucuronic acid is a direct precursor of the pentose. Thus, this experiment provides information concerning the impairment in pentosuria, and also adds further support to the concept that the glucuronic acid oxidation pathway functions in normal individuals.

3. Serum and Urinary Pentose Levels[16]*:* Studies were recently undertaken to exclude the unlikely possibility that there might be a defect in renal tubular reabsorption of pentose in individuals with pentosuria. We also wished to determine whether any abnormality in glucuronic acid metabolism could be demonstrated in subjects heterozygous for the pentosuria gene. To explore these questions we employed a specific and sensitive enzymatic assay for L-xylulose[17] in the plasma and urine of six non-Jewish control subjects, three individuals with pentosuria, and five close relatives of pentosurics, before and following the oral administration of "loading doses" of glucuronolactone. The results of these studies are summarized in table 2.

TABLE 2

Serum and Urine L-Xylulose before and after D-Glucuronolactone

	Serum Pentose		Urine Pentose	
	Before	After	Before	After
	Mg. per 100 ml.		Mg. per hour	
Pentosurics				
A	1.2	7.2		320
B	1.3	9.9	106	549
C	1.7	14.7	88	450
Pentosuric Relatives				
D	0.18	0.71	0	81
E	*	0.77		
F	*	1.26	0	
G	*	1.41	0.1	63
H	*	3.90	0	
Controls (6)	*	* to 0.29	0	3 to 22

* Less than 0.1 mg. per 100 ml.

Fasting serum L-xylulose levels in all three pentosurics were in excess of 1 mg. per 100 ml., while in the sera of all but one of the other individuals no xylulose was detectable in the fasting state. In all but two subjects, glucuronolactone led to a rise in serum xylulose levels, with a peak generally reached within one hour of feeding. The rise in serum pentose level was accompanied by a marked increase in urinary pentose in the pentosurics, and by the appearance of urinary pentose in all other subjects tested. The post-glucuronolactone serum levels of five pentosuric relatives (D, E and H in table 2 are parents of pentosurics, F is a brother of three individuals with pentosuria, and G is the son of a pentosuric) were considerably higher than those of the control subjects, and the urine levels in two pentosuric relatives were considerably greater than those in the controls. Using glomerular filtration rates calculated from creatinine clearances, we found that a major portion of filtered pentose is excreted by all individuals, pentosuric and nonpentosuric alike. Thus, these data rule out the possibility that a

renal lesion is the defect in pentosuria, but are in accord with previous studies pointing to an abnormality in L-xylulose metabolism. In addition, the higher post-glucuronolactone pentose levels in the serum and urine of the pentosuric relatives as compared with control subjects indicate that when the glucuronic acid oxidation pathway is "stressed," a metabolic abnormality can be demonstrated in individuals with pentosuria trait. This observation is in keeping with a growing body of evidence indicating that, under appropriate conditions, a chemical aberration can be demonstrated in individuals heterozygous for any of several inborn errors of metabolism.

Since pentosuria is a benign as well as an uncommon disturbance, and since the enzymes involved in L-xylulose metabolism are believed to be present only in liver and kidney, opportunities to define the abnormal site with precision will be exceedingly rare. However, the evidence summarized, although indirect, surely points to a defect in the glucuronic acid oxidation pathway of carbohydrate metabolism. In addition, pentosuria may be considered to be another in a growing series in which the study of an accident of nature has helped immeasurably in the elucidation of a metabolic pathway in normal individuals.

Summary

Pentosuria is an uncommon and innocuous inborn error of metabolism, occurring almost exclusively in Jews, and characterized by the urinary excretion of 1 to 4 gm. of L-xylulose daily. It results from a block in the glucuronic acid oxidation pathway of carbohydrate metabolism. Evidence has been cited for the operation of this pathway in normal individuals, and for an impairment in individuals with pentosuria and pentosuria trait.

Summario in Interlingua

Pentosuria es un innate error del metabolismo, characterisate per le excretion urinari de *L*-xylulosa, occurrente quasi exclusivemente in judeos e hereditate de maniera recessive autosomal. Illo resulta presumitemente de un defecto del via de oxydation de acido glucuronic in le metabolismo de hydrato de carbon in que *L*-xylulosa es un intermediario. Nos ha obtenite un forte supporto pro iste hypothese in 4 subjectos pentosuric, 5 subjectos con le tracto de pentosuria, e plure subjectos de controlo in le sequente studios:

1. Essayage enzymatic de *L*-xylulosa seral e urinari. Individuos pentosuric in stato jejun habeva nivellos seral de *L*-xylulosa de inter 1,2 e 1,7 mg per 100 ml. Iste nivellos montava a valores multiple post cargation oral con glucuronolactoma (que es un precursor de *L*-xylulosa). Nulle *L*-xylulosa esseva detegibile in le sero o le urina de subjectos normal o heterozygotic in stato jejun. Post le administration de 25 g de glucuronolactona, le nivellos seral de *L*-xylulosa variava inter infra 0,1 e 0.29 mg per 100 ml in subjectos normal e inter 0,71 e 3,9 mg per 100 ml in subjectos heterozygotic. Post le administration de glucuronolactona le heterozygoticos exhibiva similemente nivellos urinari de pentosa inter le nivellos in subjectos normal e le nivellos in subjectos pentosuric. Assi nostre datos demonstra un expression chimic del stato heterozygotic. In plus, le datos suggere que le plus grande parte del pentosa que entra in le filtrato glomerular es excernite.

2. Post le administration de glucuronolactona uniformemente marcate con carbon^{14}, sex vices plus CO_2 radioactive appareva in le aere expirate per un subjecto normal que in illo expirate per un subjecto pentosuric. Iste differentia supporta le conception que solmente un del sex atomos de carbon in le molecula de acido glucuronic pote esser metabolisate per le subjecto pentosuric qui excerne alora le remanente cinque atomos in le forma de *L*-xylulosa.

3. Per medio de un methodo que trappa le ribosa urinari, il esseva possibile monstrar que le carbon de glucuronolactona entra in le currente major del metabolismo de hydrato de carbon in le caso de subjectos normal sed non progrede in ultra del stadio de *L*-xylulosa in le caso de subjectos pentosuric.

Ben que le defecto enzymatic in pentosuria ha non ancora essite demonstrate, le factos nunc disponibile indica con alte grados de probabilitate un bloco in le via de oxydation de acido glucuronic al puncto del reaction que deberea resultar in le conversion de *L*-xylulosa in xylitol.

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CASE REPORTS

WALDENSTRÖM'S MACROGLOBULINEMIA WITH CRYOGLOBULINEMIA *

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PRIMARY macroglobulinemia is a rare disease which was first described in 1944 by Waldenström.[1] Using the ultracentrifuge, he identified abnormal proteins with high sedimentation constants in two patients who had many findings similar to those seen in multiple myeloma. The distinctive features of these cases were anemia, epistaxis, slight lymphadenopathy, lymphocytoid cells in the bone marrow, generalized osteoporosis, and the presence of macroglobulins in the serum. In one of these patients the abnormal globulin also was found to be a cryoglobulin. Since the original description by Waldenström, at least 40 similar case reports have appeared, particularly in the foreign literature. In 1956 Quattrin et al.[15] reviewed the literature on macroglobulinemia. That same year Mackay et al.[11] published a very complete article on cryoglobulinemia and macroglobulinemia. In addition to reporting five cases, they reviewed the literature and tabulated the known cases of proved, marked cryoglobulinemia. In a careful survey of the literature 16 cases were found where both cryoglobulins and macroglobulins had been proved.[1-14] Apparently some, but not all, macroglobulins become so viscid with decreasing temperature that they form a gel, and thus resemble one type of cryoglobulin.

This paper reports a case where the abnormal protein has been proved to be both a macroglobulin and a cryoglobulin, and where the findings are very similar to those in Waldenström's original description of the disease.

CASE REPORT

A 67 year old white woman was admitted to the hospital on June 18, 1956, because of severe epistaxis. She had had a recent cold and cough. Despite packing, the nosebleed continued intermittently for 14 days, and the patient received six units of blood. Physical examination revealed a blood pressure of 140/90 mm. of Hg, negative findings in the chest, and no splenomegaly, hepatomegaly or lymphadenopathy. The patient did show fairly marked arthritic changes in the hands, with fusiform swelling of the proximal interphalangeal joints and ulnar deviation of the hands. There were no petechiae or purpura. X-rays showed generalized osteoporosis, somewhat more obvious in the skull films. On admission the hemoglobin was 8.6 gm.; hematocrit, 25%; white blood cell count, 13,200, with 59 polymorphonuclears, 40 lymphocytes and 1 eosinophil; platelets, 264,000; bleeding time, 4 min. (Ivy);

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clotting time, 7 min. (Lee and White); prothrombin time, 70% of normal; prothrombin consumption, 90 sec. (control, 58 sec.), normal clot retraction, without lysis. The urine showed a specific gravity of 1.022, an albumin of 1 plus, and an occasional red blood cell, white blood cell and hyaline cast. Bence Jones protein was positive on one occasion. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was nonreactive. The

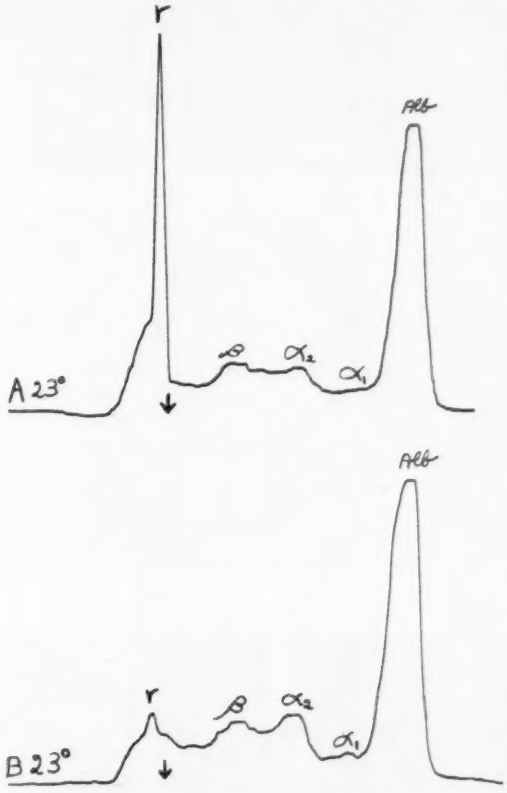

FIG. 1. A. Paper electrophoresis of whole serum at 23° C. Arrow shows point of application of serum, with practically no migration of the gamma globulin. B. Paper electrophoresis of supernatant serum after cryoglobulin had been removed by centrifugation.

total protein was 8.7 gm.% (3.4 gm.% albumin, 5.3 gm.% globulin). Paper electrophoresis was done at 23° C. and 37° C. Marked elevation of the gamma globulin fraction was present at both temperatures, but there was practically no migration of this abnormal protein at 23° C., due to the viscidity of the protein at this temperature (figure 1). Cryoglobulin was present which formed a gel precipitate at 26° C. and redissolved at 37° C. When this cryoglobulin was removed by centrifugation the electrophoretic pattern of the supernatant serum showed no elevation of the gamma globulin (figures 1 and 2). The Sia water test for macroglobulins was

positive. Ultracentrifugation of the whole serum showed, besides the usual albumin-globulin peak, two components with large molecular weights, having S_{20} values of 13.2 and 18.7 (figure 3). Ultracentrifugation of the supernatant serum obtained after removal of the cryoglobulin fraction showed only one small component of large molecular weight (S_{20}, 13.2), while study of the sedimented cryoglobulin showed the large molecular components described above (figure 4).

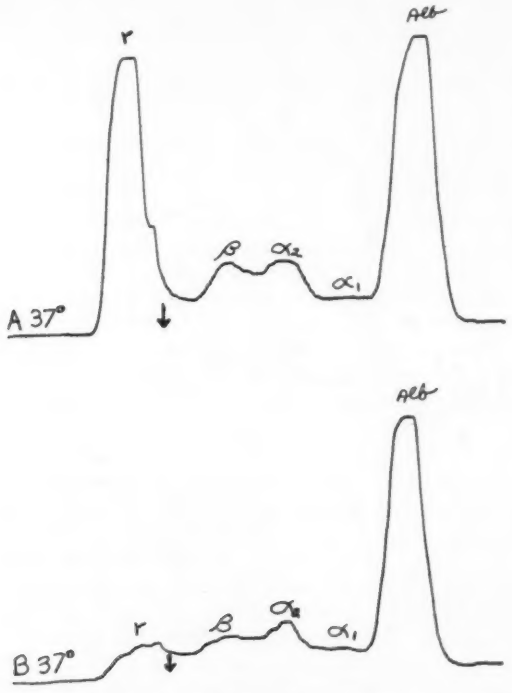

FIG. 2. A. Paper electrophoresis of whole serum at 37° C. Arrow shows point of application of serum, with migration of the gamma globulin. B. Paper electrophoresis of supernatant serum after cryoglobulin had been removed by centrifugation.

Bone marrow was aspirated from the sternum with difficulty, and the specimen was diluted with peripheral blood. However, a few marrow particles, which consisted almost entirely of small lymphocytoid cells that occasionally resembled plasma cells, were obtained (figure 5). In the diluted areas a few normal cell elements were seen, showing an increased percentage of nucleated red blood cells.

This patient's hemoglobin on discharge from the hospital in July, 1956, was 9.3 gm. She did fairly well until December, 1956, when she began to have a further progression of the arthritic changes in her hands, and progressively severe radicular pain of the chest. X-ray showed increased osteoporosis. She was hospitalized in January, 1957, and received x-ray therapy to her spine in an effort to relieve her pain. She also received three transfusions because her hemoglobin had fallen to 7.1 gm. Enlargement of the liver was noted for the first time. Bence Jones protein

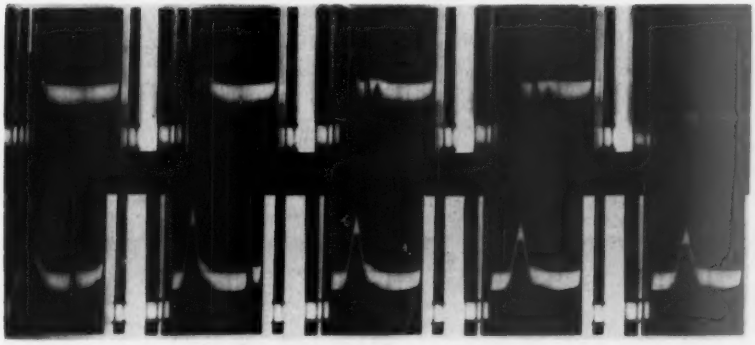

FIG. 3. Ultracentrifugal analysis of whole serum (0.2 ml. serum plus 0.8 ml. normal saline) at 38° C. and 59,780 r.p.m. First five exposures at a bar angle of 40° and 4-minute intervals. Second five exposures at a bar angle of 50° and 8-minute intervals. Note usual albumin-globulin peak plus two rapidly sedimenting components (S_{20}, 13.2 and 18.7).

was again positive, and the total protein was 10.8 gm.% (albumin, 3.2 gm.%; globulin, 7.6 gm.%).

The patient was re-admitted in March, 1957, with very severe pain in the chest cage, for which she was treated symptomatically. She has been followed at home for three years since this admission and has had no epistaxis. Her arthritis is much improved, but she continues to have moderate pain in the chest cage periodically, and has an advancing dorsal kyphosis. She received an intermittent course of Chlorambucil (6 mg. daily for a total of six weeks), from September to December, 1957, and has seemed to improve symptomatically. The total protein was 8.7 gm. on December 27, 1957. Cryoglobulins were still present, and the Sia water test was still positive. At the present time the patient is only slightly anemic (hemoglobin, 11.5 gm.).

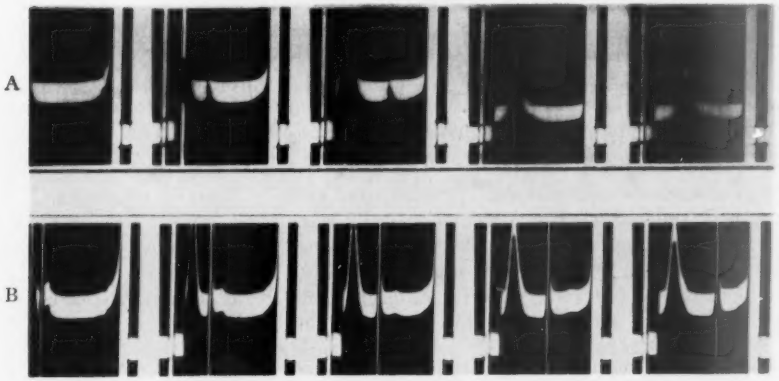

FIG. 4. A. Ultracentrifugal analysis of supernatant serum after cryoglobulin had been sedimented out. Exposures at 8-minute intervals. Note only one small, rapidly sedimenting component (S_{20}, 13.2). B. Ultracentrifugal analysis of sedimented cryoglobulin. Exposures at 4-minute intervals. Note presence of both rapidly sedimenting components.

Discussion

The syndrome of Waldenström's macroglobulinemia affects both sexes, but apparently occurs more frequently in males over 50 years of age. A hemorrhagic diathesis, frequently nasal, or other mucosal bleeding has been the initial significant complaint in many instances, although this does not have to be present. Lassitude, weakness, weight loss and pallor have often been noted. Hepatomegaly, splenomegaly and lymphadenopathy have been frequent findings. Anemia and hyperglobulinemia are characteristic, and the presence of giant pro-

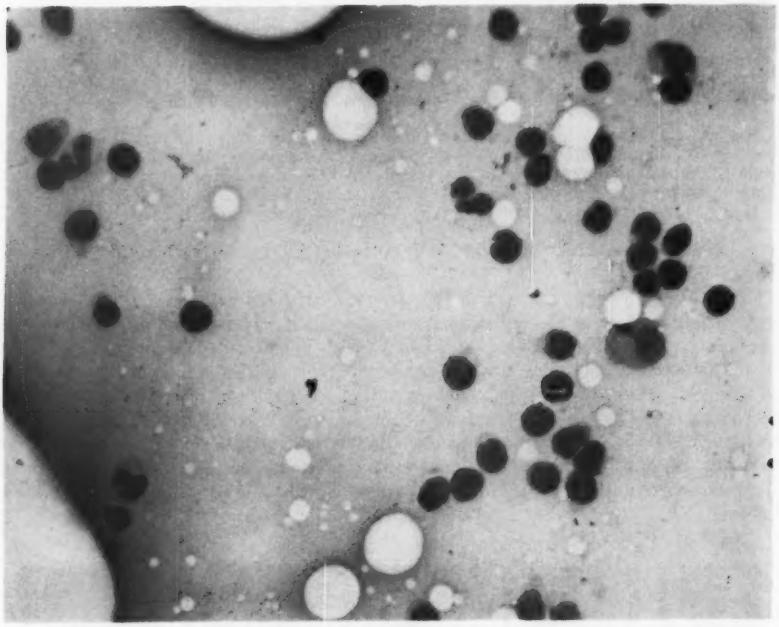

Fig. 5. Photomicrograph of Wright's stained smears of bone marrow. Note the lymphocytoid cells, some of which show shedding cytoplasm, and an occasional typical plasma cell.

tein macromolecules is diagnostic. The marrow has been described variously with phrases such as containing "lymphocytoid cells," [1] "histioid hyperplasia," [15] "lymphoid reticulosis" [16] and "lymphoid cells resembling transitional forms between lymphocytes and plasma cells." [8, 17] There usually are no punched-out bone lesions, such as are seen in multiple myeloma, but instead there is diffuse osteoporosis. Bence Jones protein has been found in the urine in a few cases. In most cases the abnormal protein has been found to migrate electrophoretically as a gamma or beta globulin, or in an area between normal gamma and beta, near normal fibrinogen. The positive Sia water test suggests macroglobulins, but it may be falsely negative or positive. Laurell et al.[18] suggest that a positive Sia water test is given by those serums which contain gamma macroglobulins, while the beta macroglobulin serums give negative tests.

The patient reported here was first hospitalized because of a severe epistaxis which could not be stopped by any of the usual measures. Questioning revealed that she had had weakness and arthritis for several months prior to the hospital admission. A protein abnormality was first suspected when her serum formed a gel when kept in the blood bank refrigerator. This gel was found to show the typical reversible cold gelification of a cryoglobulin. The Sia water test performed at 37° C. was positive, which suggested a macroglobulin. This prompted the further protein studies which showed an elevated total protein of 8.6 gm., a sharp peak of gamma globulin on electrophoresis, and two heavy components on ultracentrifugation (S_{20}, 13.2 and 18.7). The finding of a gamma globulin and a positive Sia water test is in keeping with the observations of Laurell et al.[18] Immunologic studies on this macroglobulin were not carried out. The marrow findings were compatible with most of the published descriptions of marrow in this disease, as there was almost complete replacement with cells resembling more often lymphocytes with shedding cytoplasm, but occasionally plasma cells. The patient has had a persistent anemia and considerable radicular pain in the chest. Her rheumatoid arthritis has persisted, but has been of variable severity. In the literature, reference to rheumatoid arthritic changes in this disease has not been made.

The true diagnostic significance of these abnormal globulins is not understood, but investigations into electrophoretic, ultracentrifugal and immunologic studies have contributed much to their recognition.

Macroglobulins can be definitely detected only by ultracentrifugal analysis, though Vogler et al.[19] have suggested another method combining electrophoresis and diffusion measurements. Silberman [20] also reports that macroglobulin sera can be differentiated from myeloma sera by the starch-gel method of electrophoresis. The S_{20} values of the various proteins as determined by ultracentrifugation are albumin 4.5, globulin 7, most macroglobulins 19 to 20, Bence Jones protein 2.8 to 3.4, cryoglobulin 6 to 30, and multiple myeloma proteins 6 to 8.[21, 22] A small percentage of macroglobulins (up to 5%) may be found in normal serum. Low concentrations have been reported in nephrosis, liver disease and lupus erythematosus.[11] When larger amounts are found, the macroglobulin frequently sediments out as multiple components, as in the case presented here. Serums of patients with typical multiple myeloma have seldom been reported to show macroglobulins, and x-rays of patients with macroglobulinemia do not show focal bone lesions, but some authors consider macroglobulinemia to be a variant of multiple myeloma.[23] Immunologic studies with macroglobulins have shown these abnormal proteins to be of individual immunologic specificity, differing from normal serum proteins.[24, 25, 26]

Cryoglobulins [27, 28] include a diverse group of serum globulins that have in common the physical property of reversible precipitation, crystallization, or jelling upon cooling. When the abnormal globulin is a macroglobulin, gel formation commonly occurs, but seldom precipitation or crystallization. However, not all macroglobulins behave as cryoglobulins. Mackay [29] reviewed 25 cases of macroglobulinemia, of whom 15 had cryoglobulins, 15 a positive Sia water test, and five had Bence Jones proteinuria. Apparently cryoglobulins are almost always associated with some disorder, most often with multiple myeloma or idiopathic cryoglobulinemia. They also have been found in chronic lymphatic leukemia,

lymphosarcoma and subacute bacterial endocarditis. Cryoglobulins may range from alpha to gamma globulins, electrophoretically.[11] There is no uniformity in the sedimentation constants, iso-electric points, solubilities, or other physical properties of the cryoglobulins thus far studied.[13] Cryoglobulin antisera have been produced which showed cross reaction with normal whole serum and gamma globulin but not with albumin.[11]

It is difficult to determine the over-all clinical effects of these abnormal proteins. Jim and Steinkamp [30] described a patient with macroglobulinemia who had prolonged bleeding time, prolonged clotting time, prolonged prothrombin time, decreased AC globulin and convertin, poor prothrombin consumption, and low fibrinogen. Cryoglobulinemia may be associated with no symptoms, or with cold sensitivity, purpura and Raynaud's phenomenon.[24]

Summary

1. A case of Waldenström's macroglobulinemia is described where the abnormal protein is both a macroglobulin and cryoglobulin.

2. The diagnostic aspects and possible significance of these two types of abnormal proteins are discussed.

Dr. H. E. Edelhoch and C. R. Wilcox, of the University of Kansas Medical Center, kindly did the ultracentrifugal analysis of this serum. K. S. Bowman, of the Wadsworth Veterans Administration Center, did the special paper electrophoretic studies.

Summario in Interlingua

Macroglobulinemia primari es un morbo rar que esseva primo describite in 1944 per Waldenström. Le aspectos distinctive del morbo es anemia, epistaxis, leve grados de lymphadenopathia, cellulas lymphocytoide in le medulla ossee, osteoporosis generalisate, e le presentia de macroglobulinas in le sero. Macroglobulinas es globulinas anormal de alte peso molecular. Illos pote esser detegite definitemente solmente per ultracentrifugation analytic. Le majoritate de illos ha valores S_{20} de inter 19 e 20. Illos pote esser suspicite per le demonstration de positivitate in le test de Sia. Certe macroglobulinas, ben que non omnes, deveni si viscose in le presentia de un declino de temperatura que illos forma un gel e resimila assi un typo de cryoglobulina.

Es reportate un caso in que il esseva provate que le proteina anormal esseva tanto un macroglobulina como etiam un cryoglobulina. Un scrutinio del litteratura discoperiva 16 simile casos. Le patiente esseva un femina de racia blanc de 67 annos de etate qui se presentava con sever epistaxis. Illa manifestava le constatationes typic de anemia, osteoporosis generalisate con infiltration lymphocytoide del medulla, e hypergammaglobulinemia. Le ultracentrifugation del sero revelava duo macroglobulinas con valores S_{20} de 13,2 e 18,7. Le test de Sia esseva positive. Le sero formava un gel a 26 C, con re-solution a 37 C. Symptomaticamente le patiente pareva meliorar se post un curso de Chlorambucil.

Le ver signification diagnostic de iste globulinas anormal non es clar. Reportos del constatation de macroglobulinas in myeloma multiple es rar, sed cryoglobulinas es associate frequentissimemente con iste morbo. In le majoritate del casos on ha trovate que le migration electrophoretic del macroglobulina esseva illo de un globulina gamma o beta o que illo se rangia in un area inter le normal globulinas gamma e beta. Cryoglobulinas pote variar ab alpha a gamma, e le valores S_{20} de illos es inter 6 e 30. Macroglobulinas possede specificitate immunologic individual, sed antiseros anti cryglobulina exhibi reaction cruciate con sero total e con globulina gamma. Il es defficile determinar le effecto clinic general de iste proteinas anormal.

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PLASMA THROMBOPLASTIN COMPONENT DEFICIENCY IN THE EHLERS-DANLOS SYNDROME *

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Introduction

The Ehlers-Danlos syndrome, fully described in a recent monograph by McKusick,[1] is a rare, congenital, hereditary disorder of the connective tissue with clear-cut clinical manifestations. Abnormal bleeding in this syndrome occurs frequently,[2, 3] and in some patients the hemorrhagic condition may be the prominent abnormality; Samuel et al.[4] reported a 32 year old female who gave a history of vaginal, rectal, nasal and cutaneous bleeding. The prominence of the bleeding in some cases led McKusick to state that this syndrome "must be included in the differential diagnosis of familial hemophilia-like states." The consensus regarding the physiopathology of the hemorrhagic tendency favors capillary fragility as the chief cause. However, this conclusion seems to have been drawn on the basis of negative routine blood clotting tests,[5] since specialized studies of the blood coagulation mechanism apparently have not been done in patients with this disorder.

The purpose of this paper is to report the abnormalities in the blood coagulation mechanism demonstrated by means of the thromboplastin generation

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test in two related patients with the Ehlers-Danlos syndrome. Both had a clotting defect due to a deficiency in the plasma thromboplastin component.

Case Reports

Case 1. An 11 year old white female had been observed since shortly after birth to have a very smooth, thin skin and hyperextensibility of the joints, causing frequent luxations of the shoulders. As soon as she began to walk her mother noticed easy laceration and poor healing of the skin after minor trauma.

Fig. 1. *Case 1.* Hyperelasticity of the skin over the elbow regions.

The patient had had a tonsillectomy at age four without unusual bleeding; easy bruising and hematomas following venipunctures had been present all of her life. Her family history was very interesting: her mother, two maternal aunts, and her maternal grandmother and greatgrandfather had all had a similar skin condition. The latter, in addition, had been known to be a "bleeder."

Physical examination revealed hyperelasticity of the skin, particularly over the elbows (figure 1), numerous hyperpigmented scars on the forehead and lower extremities, with molluscoid pseudotumors over the knees (figure 2), hyperextensibility of the joints (figures 3 and 4), and some peculiar neurologic findings, characterized by the presence of superficial anesthesia in both lower extremities extending up to the middle of the thighs.

Laboratory data: The following tests were normal or negative: complete blood count, urinalysis, fasting blood sugar, blood urea nitrogen, liver function tests, chest x-ray and electrocardiogram. Routine clotting studies were also normal (table 1). Biopsy of skin taken from the left leg revealed a thinned epidermal layer and the

FIG. 2. *Case 1.* Hyperpigmented scars on both lower extremities.

FIG. 3. *Case 1.* Hyperextensibility of the first metacarpophalangeal joint.

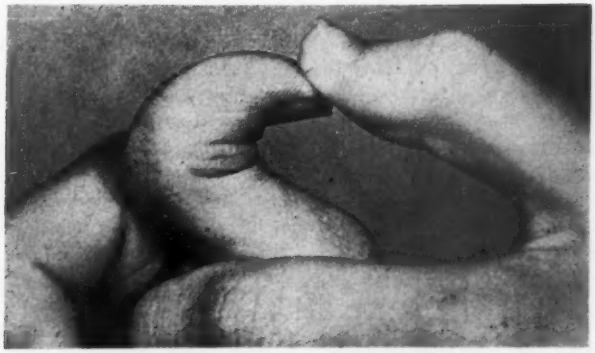

FIG. 4. *Case 1.* Hyperextensibility of the interphalangeal joints.

presence of numerous elastic fibers in the dermis, a picture consistent with the diagnosis of Ehlers-Danlos syndrome.

Case 2. A 54 year old white female, mother of the former patient, had since childhood had a very thin and fragile skin and hyperextensibility of the joints. Skin wounds healed very poorly, leaving hyperpigmented, atrophic scars. Easy bruising had been present all of her life, but she had withstood several tooth extractions, and had delivered one child without any untoward bleeding.

Physical examination disclosed skin and joint abnormalities similar to those in her daughter. The results of routine clotting tests are shown in table 1.

Special studies: Figure 5 shows the results of the thromboplastin generation tests done on both patients. Both patients had a defect in the serum fraction that, when crossmatched with known plasma thromboplastin component and Stuart factor-deficient serums, was shown to be due to a deficiency of plasma thromboplastin component.

DISCUSSION

The presented data seem to establish the presence of a plasma thromboplastin component deficiency in two related patients with the Ehlers-Danlos syndrome. This situation brings up a few interesting points which we will discuss briefly.

These two cases again show that routine clotting tests are not sufficient to rule out the presence of clotting factor deficiencies, particularly of those deficiencies participating in the first stage of blood clotting.[6] The findings reported in this paper cast doubt on the statement that bleeding in the Ehlers-Danlos syndrome is always a result of vascular defects. It seems, then, that clotting

TABLE 1

Routine Clotting Tests

Tests	Case 1	Case 2
Whole blood clotting time (normal, up to 20′)	10′	11′
Plasma recalcification time (normal, 90 to 160″)	130″	100″
Bleeding time (normal, up to 5′)	1′	2′
Platelet count (normal, 200,000 to 400,000)	308,000 × mm.^{3}	210,000 × mm.^{3}
Prothrombin time (control, 13″)	14″	13″
Serum prothrombin time (normal, over 20″)	42″	35″
Fibrinogen (normal, 200 to 500 mg. × 100 ml.)	225 mg. × 100 ml.	205 mg. × 100 ml.

studies more sensitive than the routine ones should be performed in every case of Ehlers-Danlos syndrome, especially in patients with a hemorrhagic tendency. We believe that this point has more than academic interest, because the existence of a clotting abnormality may require modifications in the management of these patients, particularly if they have to undergo surgery.

The situation in our patients resembles that seen in the varieties of pseudohemophilia described as vascular hemophilia [7] and pseudohemophilia type B.[8] In these varieties a vascular defect occurs in association with deficiency in anti-

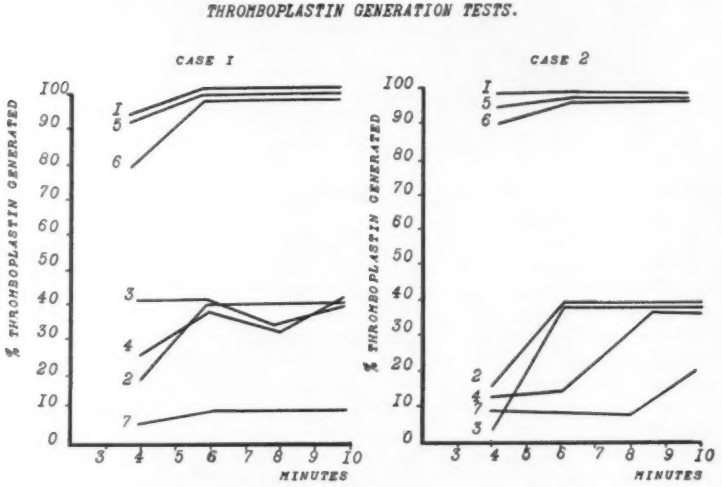
THROMBOPLASTIN GENERATION TESTS.
CASE 1
CASE 2
% THROMBOPLASTIN GENERATED
MINUTES
1.- NORMAL SYSTEM.
2.- PATIENT'S SYSTEM.
3.- PATIENT'S PLATELETS AND SERUM + NORMAL PLASMA.
4.- PATIENT'S PLASMA AND SERUM + NORMAL PLATELETS.
5.- PATIENT'S PLATELETS AND PLASMA + NORMAL SERUM.
6.- PATIENT'S PLATELETS AND PLASMA + 1:1 MIXTURE OF PATIENT'S AND STUART FACTOR DEFICIENT SERUMS.
7.- PATIENT'S PLATELETS AND PLASMA + 1:1 MIXTURE OF PATIENT'S AND PTC DEFICIENT SERUMS.

FIG. 5. Thromboplastin generation test, showing that both patients have a plasma thromboplastin component deficiency, as proved by curve #7.

hemophilic globulin, plasma thromboplastin component and other clotting factors.[9] This resemblance makes one wonder if adequate studies will not show that the Ehlers-Danlos syndrome may be associated with deficiencies other than that of plasma thromboplastin component.

From the genetic standpoint, plasma thromboplastin component and antihemophilic globulin deficiencies behave similarly, in that the abnormal gene is carried in the X chromosome. However, they differ in that, in the former, the heterozygous female can either: (a) be clinically asymptomatic, and with a normal plasma thromboplastin component concentration; (b) be clinically asymptomatic, but with plasma thromboplastin component deficiency demonstrated by the thromboplastin generation test; or (c) have laboratory and clinical manifestations

of the disease. The first type is the most common, but there are some reported cases that, like our two patients, belong to the second category.[10] The third variety of heterozygous females is apparently very rare.[11] Ramot et al.[10] believe that the variability in the clinical expression of the plasma thromboplastin component deficiency in females may be due to the presence of a modifier gene. The latter, which is necessary for hemorrhagic manifestations to occur, would usually be located in the Y chromosome, but could occasionally be present in other chromosomes. This hypothesis explains why the plasma thromboplastin component deficiency always finds clinical expression in males, whereas female carriers, with some exceptions, are normal.

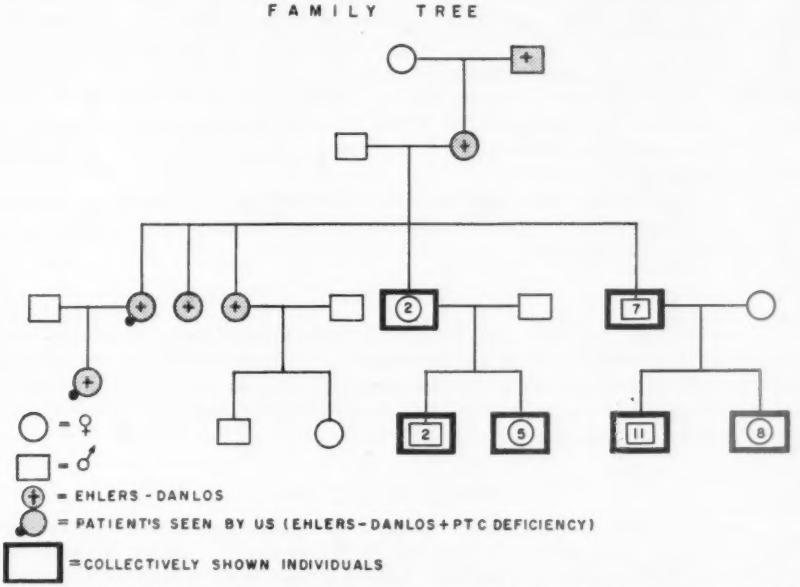

FIG. 6. Family tree. The only male affected by the Ehlers-Danlos syndrome was a "bleeder." Five females have the Ehlers-Danlos defect, and the only two studied by us had plasma thromboplastin component deficiency.

The Ehlers-Danlos syndrome is transmitted by an autosomal dominant gene of variable penetrance,[12] which explains why complete clinical expression can be seen in heterozygous patients, and why phenotypically normal individuals may pass on the disease to their offspring.

The simultaneous occurrence of two rare, inherited disorders like the plasma thromboplastin component deficiency and the Ehlers-Danlos syndrome could be explained by chance association of the abnormal genes. The family tree of our patients (figure 6) is compatible with the mode of inheritance of both abnormalities, if we assume, as seems reasonable, that the first patient's greatgrandfather had both diseases. There are, however, some facts that have not been reconciled with this explanation. Statistically, the chance association of these two rather

rare genes seems unlikely, and it is certainly unusual that the genes in question have not segregated independently. This is particularly noticeable in the third generation, in which there were seven males, none of whom appears to have shown clinical evidence of either hemophilia or Ehlers-Danlos defect. Unfortunately, none of these persons was available for study,* and it was necessary to rely on data furnished by our second patient. Other evidence seeming to indicate a lack of independent segregation of the two genes is that the only male known to have the skin abnormalities (first patient's greatgrandfather) was a "bleeder."

Linkage between the abnormal genes or, as seems more likely, interference of the abnormal gene responsible for the Ehlers-Danlos syndrome, with the expression of the gene for plasma thromboplastin component production, would explain our findings better. Singer and Ramot [8] have postulated a similar explanation for the pseudohemophilia type B. The possibility that our two patients have a male sex-chromatin pattern, as was recently described in a "girl" with hemophilia A,[13] could not be studied, but it does not seem likely, as it would be necessary to postulate that this chromosomal aberration is transmissible from generation to generation.

It is obvious that adequate study of the clotting mechanism in patients with the Ehlers-Danlos syndrome will help to clarify the genetic problem presented by our two patients.

Summary

Two patients (mother and daughter) with Ehlers-Danlos syndrome and deficiency of Christmas factor are described. The latter could be demonstrated only by the thromboplastin generation test, and had no clinical significance in these patients; however, the only male in their family with the Ehlers-Danlos syndrome was a "bleeder."

Summario in Interlingua

Le occurrentia de sanguination anormal es reportate satis frequentemente in descriptiones de patientes con le syndrome de Ehlers-Danlos. On ha attribuite iste sanguination a un augmentate fragilitate capillar, proque in iste patientes le resultatos obtenite in tests routinari del hemo-coagulation pareva esser normal.

Le mechanismo coagulatori esseva investigate in duo femininas, matre e filia, con le complete syndrome de Ehlers-Danlos. Le tests routinari del coagulation—incluse le test del tempore de prothrombina seral—esseva normal, sed le test del generation de thromboplastina revelava le presentia de un anormalitate in le sero del duo patientes, e appropriate essayos cruciate con seros a varie cognoscite deficientias solitari resultava in le constatation que le anormalitate esseva un deficientia de componente thromboplastinic del plasma. Iste anormalitate esseva sin signification clinic in le duo patientes mentionate, sed il esseva cognoscite que le bisavo del filia—a parte le facto que ille habeva habite un anormalitate cutanee—habeva essite un "sanguinator." Tres altere membros feminin de iste familia habeva le syndrome de Ehlers-Danlos sin antecedentes de sanguination anormal, sed infelicemente il non esseva possibile studiar las. Es discutite le signification genetic del observate association del syndrome de Ehlers-Danlos con deficientia de componente thromboplastinic del plasma, e le existentia del un o del altere typo de interaction es postulate inter

* The relatives of our patients are scattered throughout the world.

le genes responsabile pro le duo disordines. Studios additional de familias con le syndrome de Ehlers-Danlos es requirite ante que le formulation de conclusiones general deveni possibile.

Es signalate le similitudes inter nostre patientes e le pseudohemophiliacos con certe typos de deficientia de factor coagulatori.

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PNEUMATOSIS CYSTOIDES INTESTINALIS*

By Joseph P. Whittle, M.D., *Colonial Heights, Virginia*

Pneumatosis cystoides intestinalis was first described adequately in humans by Bang in 1876. It is characterized by the presence of multiple gas-containing cysts in the walls of the small or large intestine and, more rarely, the stomach, mesentery and retroperitoneal structures. In 1952 Koss[1] was able to collect 213 cases from the world literature. Since then a number of cases have been reported, but the condition must still be considered to be a rarity.

The following case is reported chiefly because it illustrates the feasibility of establishing this diagnosis by sigmoidoscopic and radiologic means and thereby avoiding unnecessary surgical exploration.

* Received for publication February 25, 1959.
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Case Report

Present Illness: A 68 year old white woman was first seen as an office patient and admitted to the Petersburg General Hospital in July, 1958. She complained of intermittent attacks of diarrhea, accompanied by lower abdominal cramping and

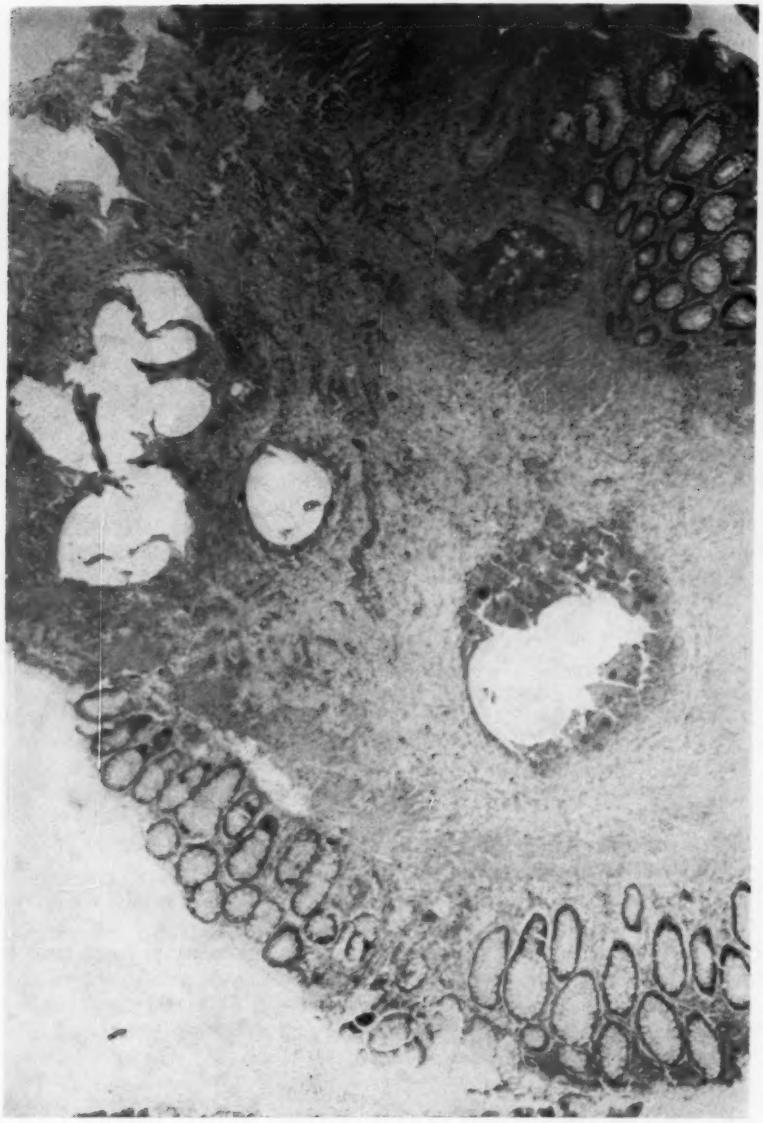

Fig. 1. A low power view of rectal mucosa, with microcystic spaces, granulomata and a microsinus in the right upper corner. (× 50)

FIG. 2. Break in continuity of mucosa, with microsinus (A) and granuloma (B) in submucosa. (× 100)

flatulence of six months' duration. Prior to this she had had a lifelong tendency to constipation. The stools had not contained blood or pus. Appetite and body weight had not been affected.

Past History: Two years before she had had several bouts of paroxysmal auricu-

lar fibrillation. During this time she had also complained of ill-defined epigastric discomfort. Laboratory tests at that time had included a normal cholecystogram and an upper gastrointestinal series. Her symptoms improved after treatment with digitalis and Pronestyl. Medication for the last year had consisted of digitoxin, 0.1 mg.

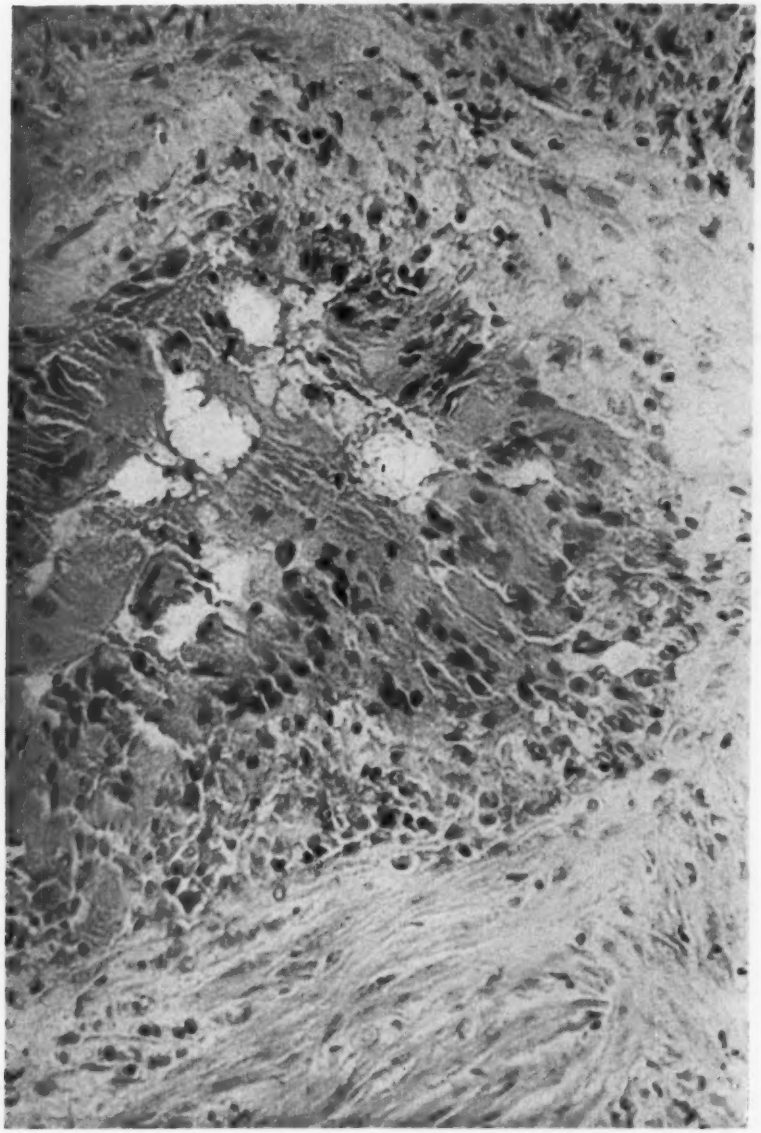

FIG. 3. High power view of granuloma in the submucosal layer, showing giant cells and breakdown of tissue suggesting beginning of cyst. (× 430)

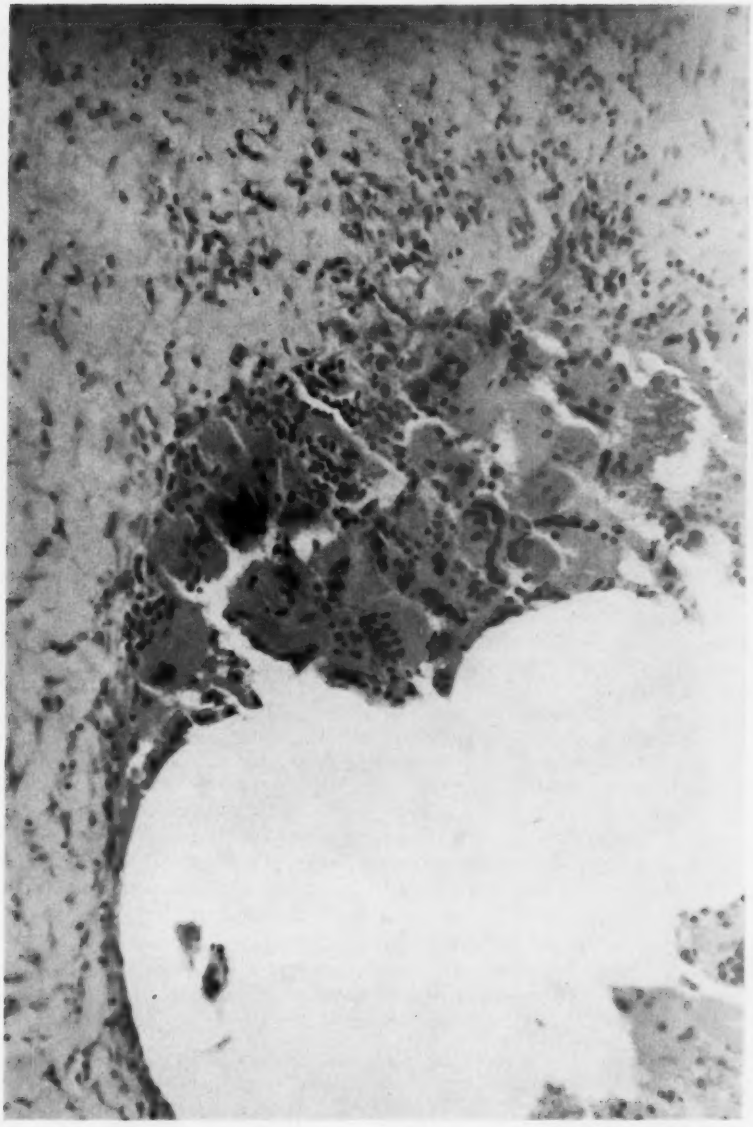

FIG. 4. High power view, showing edge of cystic structure in intestinal wall. (× 430)

daily, Pronestyl, 250 mg. three times a day, and Atarax, 25 mg. three times a day. There had been no recurrence of fibrillation, and epigastric symptoms had not been troublesome during the last 12 to 18 months.

Physical Examination: On admission, examination revealed a somewhat underweight elderly woman in no distress. The abdomen was not distended or tender.

Bowel sounds were normal. No masses or organs were palpable. The remainder of the physical examination, including a digital examination of the rectum, was negative.

On sigmoidoscopy, beginning in the rectal ampulla the mucosa presented a "cobblestone" appearance, consisting of multiple rounded elevations covered with slightly pale but otherwise normal mucosa. These were fairly uniform, being approximately 7 to 10 mm. in diameter. The initial impression was multiple polyposis.

Laboratory Studies: Routine studies of blood and urine were within normal limits.

A barium enema study on the day following admission showed multiple filling defects affecting the large bowel as far proximally as the hepatic flexure. The ascending colon and terminal ileum were visualized and showed no involvement. The initial interpretation of these films was in agreement with the clinical diagnosis, i.e., polyposis of the colon. At a later date an upper gastrointestinal series, which included interval films to show the small bowel, was interpreted as normal.

On a repeat sigmoidoscopy, biopsies were taken of several of the accessible moundlike elevations. Histologic sections of the biopsy material showed several fragments of rectal mucosa and submucosa (figure 1). The epithelial lining was interrupted at a few points, and the crypts of Lieberkühn were pushed apart by microsinuses penetrating into the submucosa (figure 2, point A). The walls of the microsinuses were lined by relatively indolent granulation tissue, infiltrated by a few lymphocytes and many multinucleated giant cells of the foreign-body-reaction type. There were also several independent granulomata within the muscularis mucosae and submucosae (figures 2, B and 3). These were made up predominantly of giant cells with a few lymphocytes. The most conspicuous findings were microcystic spaces within the submucosa (figure 4). The lining of the cysts was made up of compressed and flattened connective tissue simulating endothelium. There were also foreign-body giant cells and rare lymphocytes around the cysts. Based on these microscopic findings, the diagnosis of pneumatosis cystoides involving the distal colon was established.

With this diagnosis in mind, a review of the barium enema films revealed certain significant findings which were helpful in arriving at the correct diagnosis (figures 5 and 6). The negative shadows comprising the filling defects described originally projected in part beyond the bowel wall. Also noted was the total absence of pedicles, such as would be expected in polyposis.

Clinical Course: During the patient's short hospital stay, several bouts of diarrhea were aborted by the administration of paregoric and milk of bismuth mixture. She was discharged on a low-residue diet, antispasmodic medication, and paregoric and milk of bismuth mixture to use during active diarrhea.

Following discharge, the patient continued to have a troublesome degree of diarrhea. On several occasions this was accompanied by the passage of some mucus and small quantities of blood. A barium enema study two months after the initial work-up showed no change in the appearance of the bowel.*

* Because of inability to control the symptoms of this patient satisfactorily, she was referred to Dr. Charles Caravati, in Richmond, Virginia, in September, 1958. In general, his findings confirmed those of the initial studies.

By this time, however, abdominal cramps accompanying the bouts of diarrhea had begun to be a much more important part of the clinical picture. He felt that these episodes were in reality due to fecal impaction, with partial low intestinal obstruction and leakage of fluid feces around the impaction.

On his advice, paregoric was discontinued, and an unrestricted diet and daily doses of Metamucil or a similar bulk-promoting agent were instituted. This resulted in considerably better control of symptoms.

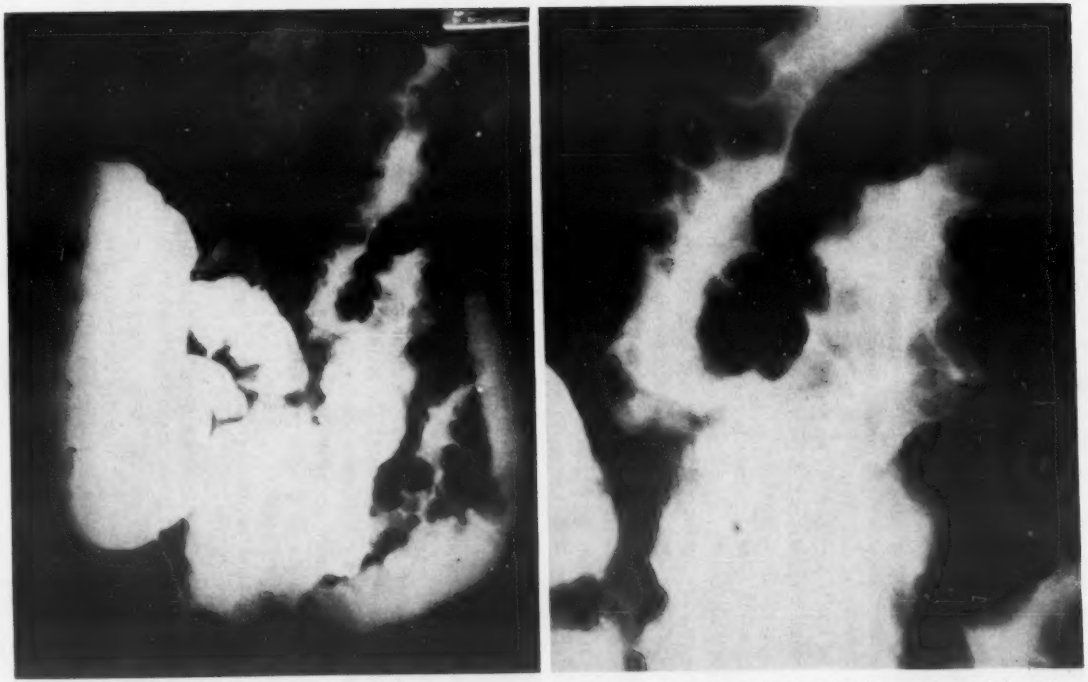

FIG. 5 (left). Barium enema, demonstrating multiple radiolucent filling defects in the distal two thirds of the colon. FIG. 6 (right). Enlargement of a segment of transverse colon, demonstrating that the defects due to gas cysts have smooth margins, marked variation in size and no associated pedicles, and that they project beyond the bowel wall.

Discussion

In 1952 Koss published the most widely quoted review of this subject. Of his 213 collected cases, 85% were secondary to a recognized underlying disease, most commonly gastric or duodenal ulcer with pyloric obstruction. The small bowel distal to the duodenum was the site of involvement in the vast majority of these cases. In the remaining 15%, the cysts were not associated with any recognizable underlying gastrointestinal disease, and were classed as "primary." The terminal ileum and cecum were most commonly involved in the primary cases, and the cysts were more often submucosal, in contrast to the predominant subserosal location in secondary pneumatosis.

The cysts vary in size from a few millimeters to the "size of a child's head." They may be multiloculated. The lining is usually formed by endothelial cells, with occasional multinucleated giant cells. The cysts contain gas and only rarely a serosanguineous fluid.

In the cases of secondary involvement, the clinical picture is usually that of the underlying disease. Complications attributable to the cysts have included spontaneous tension pneumoperitoneum due to rupture of a subserosal cyst, and intestinal obstruction due to encroachment on the bowel lumen by large clusters of cysts. More rarely reported has been volvulus or obstruction due to adhesions between the cysts. If the distal colon is involved, diarrhea, flatulence and occasionally melena may be prominent symptoms.

In 1954 Kreeger and Littman [2] reported the first American case where pneumatosis lesions were visualized by sigmoidoscopy and the diagnosis was established by microscopic sections of biopsy material. In 1957 Pemberton et al.[3] reported one case and found seven others in the world literature that had exhibited involvement of the descending and sigmoid colon. By 1958 Smith et al.[4] had collected 27 cases and reported four of their own of involvement distal to the splenic flexure. These authors were impressed by the marked increase in frequency of the distal colon involvement during recent years but were unable to offer a satisfactory explanation for this.

There is no generally accepted theory of etiology. Neoplasm and infection by gas-forming bacteria have been rejected. Trauma or nutritional deficiencies are considered by some authors to be possible causes. Several cases have been reported that appeared to develop shortly after sigmoidoscopy, but this must be considered extremely rare.

In the absence of acute complications requiring surgery, management should be conservative. This has been generally adhered to in the reported cases if the true diagnosis has been established before surgical exploration has been undertaken. Most authors have felt that the benign nature of the disease, and the occasional spontaneous disappearance of the cysts, justify a symptomatic approach.

Summary

A case of pneumatosis cystoides intestinalis is reported. Interesting features include location of the cysts in the distal colon and rectum, establishment of the diagnosis by biopsy through sigmoidoscopy, and classic radiologic findings. A review of the recent literature with relation to this case is presented.

SUMMARIO IN INTERLINGUA

Un femina de racia blanc de 68 annos de etate se plangeva de diarrhea intermittente con crampos e flatulentia de un duration de sex menses. Esseva notate nulle altere symptomas systemic. Constipation perpetue habeva precedite le declaration del presente maladia.

Le examine physic revelava nulle anormalitates significative. Studios laboratorial esseva intra le limites del norma. Sigmoidoscopia revelava—comenciante in le ampulla rectal—un mucosa coperite de multiple elevationes ronde. Le mucosa supra illos esseva normal. Un clyster a barium monstrava multiple defectos de replenation que afficeva le intestino crasse proximalmente usque al flexura hepatic. Le studio histologic del material bioptic obtenite durante le sigmoidoscopia establiva le diagnose de pneumatosis cystoide afficiente le colon distal. Un tractamento symptomatic resultava in le stabilisation satisfacente del diarrhea.

Pneumatosis cystoide intestinal es characterisate per le presentia de multiple cystes a contento gasose in le pariete del intestino tenue o crasse. Sectiones microscopic demonstra que le spatios cystic es revestite de plattificate tissu conjunctive, con multinucleate cellulas gigante e un sparse infiltration lymphocytic in le area circumdante. Un majoritate del casos reportate es secundari a chronic morbo gastrointestinal, predominantemente ulcere duodenal con obstruction pylotic. Tamen, in recente annos un crescente numero de casos "primari" ha essite reportate, specialmente con affectiones del colon. Le etiologia del condition remane obscur.

Un tractamento conservative es indicate in le casos que es diagnosticate ante le exploration chirurgic.

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INTRATHORACIC ACCESSORY LOBE OF THE LIVER*

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AN accessory or anomalous lobe of the liver is an uncommon finding which, while of little clinical importance, may present a diagnostic problem. It is usually an incidental finding in a patient with no pulmonary symptoms.

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Accessory liver lobes arise most commonly from the right lobe and may project in any direction. The most common is Riedel's lobe, which descends inferiorly along the right lateral abdominal wall as a tongue-like projection from the inferior border of the liver. Anomalous lobes arising from the superior surface of the liver present diagnostic problems, since they may appear as a rounded mass in the right lower lung field apparently arising from the diaphragm. Superior accessory lobes have no characteristic location, having been described as occurring on all quadrants of the diaphragm. There is unanimity of opinion that the best diagnostic procedure consists in establishing a pneumoperitoneum, which will indicate that the mass is below the diaphragm arising from the superior surface of the liver. This, of course, gives no indication as to the nature of the lesion, since it may be a cyst, a solid tumor, or an accessory lobe.

A review of the literature[1, 2, 3, 4] disclosed one instance of a supradiaphragmatic, intrathoracic accessory lobe of the liver. Hansbrough and Lipin[5] described a 26 year old male with a rounded mass in the periphery of the right lower lung field. Pneumoperitoneum localized it to be above the diaphragm. A thoracotomy in this case revealed a small liver lobe in the right pleural cavity, connected to the liver by a small pedicle containing an artery, a vein and a bile duct. The diaphragm was covered by intact pleura superiorly, and peritoneum inferiorly. The excised liver lobe was a pyramidal-shaped mass, 12 by 5 cm. in size and weighing 137 gm.

In the case presented in this communication, a similar liver lobe was found. The mass lay within the mediastinal pleura, above the diaphragm and connected to the liver by a pedicle that pierced the diaphragm through a small hiatus.

Case Report

The patient was a 48 year old housewife with known rheumatic heart disease. She was admitted to the hospital for evaluation for mitral commissurotomy subsequent to a recent cerebral embolus from which she had recovered. During her clinical examination she was noted to have typical changes of rheumatic heart disease with mitral stenosis. Roentgen study of the chest revealed, in addition to the cardiac abnormality and secondary pulmonary hypertension, a mass lying in the medial basal segment of the right lower lobe. This appeared to be distinct from the diaphragm, and did not change in size with breathing or variation in intrathoracic pressure. It had the appearance of a coin lesion, lying entirely within the chest. Following a thorough cardiovascular evaluation and investigation for possible sites of primary malignancy, the patient was subjected to a mitral valve commissurotomy. Fifteen days following the cardiac procedure the patient was submitted to a right thoracotomy. She tolerated both procedures well and returned home two weeks after the second operation.

Surgical exploration was done through the usual right posterolateral thoracotomy approach. A firm tumor mass was found which measured 4.4 cm. in greatest diameter. It lay within the mediastinal pleura, just lateral to the inferior vena cava, superior to the diaphragm, and anterior to the inferior pulmonary ligament. The mediastinal pleura overlying this tumor mass was incised and its surface exposed. It had the appearance of normal liver. The diaphragmatic aspect of the mass was inspected, and a pedicle was found which passed through a small hiatus to connect with the liver. The diaphragm was incised in the region of this small hiatus, and the pedicle examined. A biopsy taken from the tip of the mass was reported as normal liver tissue. The edges of the incised diaphragm were approximated, and the

FIG. 1. A round mass is seen in the medial aspect of the right lower lung field. A deep inspiration during the fluoroscopic examination separated the mass from the diaphragm.

pleural incision was closed. The remainder of the exploration of the right chest was completely normal. The patient withstood the procedure well and had an uneventful postoperative course.

Comment

The cause of accessory or anomalous lobes of the liver is not known. The embryologic development of the diaphragm suggests the origin of such a lesion. During its formation the liver lies in close relation to the developing diaphragm. The cranial portion of the septum transversum forms the diaphragm and the caudal portion, the hepatic ligaments. It is possible that a small nest of developing liver may be pinched off from the main body of the organ and come to lie above the diaphragm.

Many cases of accessory lobe have been described as arising from the superior surface of the liver, but with only one exception these have been infradiaphragmatic and easily differentiated from intrathoracic tumor. The patient reported in this communication presented all of the usual diagnostic problems associated with an isolated mass in the chest. As is often the case, the final diagnosis was made only after direct examination of the lesion. The presence of an incapacitating, remediable cardiac valvular lesion does not preclude major surgery for removal of a potentially malignant intrathoracic tumor.

Conclusion

A case of accessory or anomalous lobe of the liver in the right hemithorax is presented. This is a rare anomaly, which can present a diagnostic problem. Anomalous liver lobe should be considered in the differential diagnosis of any mass found in the right lower hemithorax.

Summario in Interlingua

Lobos accessori del hepate non es rar, sed illos se trova quasi sin exception infra le diaphragma e es facilemente differentiate ab lesiones intrathoracic per studios roentgenographic post induction de pneumoperitoneo in le patiente. Le presente reporto concerne un caso de lobo accessori del hepate a sito supra le diaphragma intra le pleura mediastinal e connectite con le massa capital del hepate solmente per un pediculo que perciava le diaphragma per un minuscule hiato. Isto es un anormalitate de extreme raritate e es explicate possibilemente como resultato de un dissecamento de un nido de hepate in stato evolvente per le portion cranial del septo transverse quando illo forma le diaphragma. Anormal lobos hepatic deberea esser considerate in le diagnose differential de nodulos solitari in le lobo dextero-inferior del pulmon a sito justo supra le diaphragma. Le diagnose pote esser confirmate solmente per le examine directe del specimen.

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PERIODIC PERITONITIS, ONSET SIMULTANEOUSLY WITH MENSTRUATION*

By JULIUS SCHWARTZ, M.D., *Brooklyn, N. Y.*

IN recent years there have been sporadic reports of a heterogeneous group of disorders which have had diverse manifestations, yet have had an outstanding characteristic in common. The appearance of recurrent attacks at regular or irregular intervals, with apparent complete recovery between the episodes, has suggested that there may be a common bond among them.

Reimann[1-5] has written extensively on this problem, and has suggested that each group be named according to its most outstanding feature, even though there is some overlapping of symptoms. The most important have been listed as periodic abdominalgia (benign paroxysmal peritonitis), periodic neutropenia and periodic arthritis. All of these, together with a few other minor recurrent disorders, have been classified as "periodic disease." Many patients suffering from this condition have undergone an enormous number of diagnostic and therapeutic procedures, usually to no avail.

Benign paroxysmal peritonitis has additional importance because of the difficulty in distinguishing it from the acute surgical abdomen resulting from acute appendicitis or acute cholecystitis. Frequent operations have been performed, either during the active stage because of this concern, or during the quiescent period, for diagnostic reasons. Siegal[6,7] reported a number of cases who demonstrated this perplexing problem. The clinical picture may be that of chills followed by abdominal pains, at first in the lower quadrant, gradually becoming more generalized. At times the most severe pain is in the upper right quadrant. Chest pains of a pleuritic type may have been present in the past or may accompany the abdominal symptoms. Severe malaise, nausea and vomiting may prostrate the patient. Fever may range from 101° F. to 105° F. Abdominal soreness and exquisite rebound tenderness are often marked.

The white cell count is usually elevated, so that a classic picture of acute peritonitis is presented. The average episode persists for two to three days, the temperature returning to normal in 48 hours. Surgical exploration was done in a number of cases during the acute stage, and although evidence of an inflammatory response, such as edema, free fluid and adhesions, was seen, no cause for the reaction was evident. In one studied case,[8] inoculation of the peritoneal fluid on aerobic and anaerobic media produced no growth, and no organisms were observed on direct smears, although many polymorphonuclear cells were present.

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The etiology of this disease remains obscure. Endocrine, allergic, infectious and psychosomatic causes have been considered, but complete investigation of many of the patients has failed to substantiate any of these possibilities. The repetitive nature of the paroxysmal abdominal pains is outstanding. The attacks may appear at irregular intervals, at first once or twice a year, with a gradual increase in frequency until recurrences are evident weekly or monthly. They may continue for years, but the general health may appear to be good during the intervals. Much speculation has been aroused by the mysterious return of these disorders, yet no satisfactory explanation has been proposed, except the presence of an unknown rhythm[9] which may be involved in the appearance of the attack. At times the episode can be anticipated, since it may return according to a time cycle of seven days or multiples of seven; at other times no exact periodicity can be noted, bouts coming on at extremely irregular intervals. Reimann states that periodic disease is not related to the menstrual cycle. A case in which occurrence of attacks of peritonitis came on only in association with menstruation is therefore of interest.

Case Report

A 29 year old white Jewish female, born in the United States, was admitted to the hospital for investigation of recurrent attacks of abdominal pain. Mother and father had been born in Syria and were living and well. Antecedents had lived in Syria for many generations. No other member of the family had any chronic recurrent disorder. System review was noncontributory. Menstruation had begun at 13 years of age and appeared regularly every 28 days, with no difficulty until the onset of the present illness. An appendectomy had been performed at an early age.

The first intimation of the future difficulty occurred in 1947 with an attack of pleurisy, which reappeared at irregular intervals for several years, averaging about one yearly. Radiologic examination of the chest was consistently normal.

In 1951 the initial episode of abdominal pain appeared one day post partum, after a normal delivery of the patient's second child. Since then, attacks had recurred at intervals, each reappearance being intimately associated with the menstrual flow, the first symptom becoming manifest within 24 hours. No definite patterns of recurrence have been observed, episodes occurring with a single menstrual period or with several successively in a row. Cessation of all attacks occurred during a pregnancy, following which an increased frequency was noted. Most attacks were similar to others, and had typical symptomatology each time.

About 12 to 24 hours after the onset of the menstrual flow, the patient begins to have abdominal soreness, usually starting in the lower quadrants and then gradually spreading upward to become more generalized. Pain is constant and generally increases markedly in intensity, with occasional superimposed cramping sensation. Shaking chills occur early, with rise in temperature to 103° F. to 105° F. Nausea and vomiting are almost always present.

On physical examination during the attack, the patient appeared to be acutely ill, lying on her side with legs drawn up. Any movement aggravated the abdominal pain. No abnormality was noted in the heart or lungs. The abdomen was somewhat distended, with marked generalized tenderness and exquisite rebound pain. This was so severe that the patient required Demerol injections for relief. She appeared to have a classic acute peritonitis. This condition remained for one or two days, when the temperature gradually returned to normal levels, with complete subsidence of all symptoms.

Physical examination at the hospital in an asymptomatic interval revealed a thin, poorly developed white female in no distress. Heart and lungs were normal. The

abdomen was soft, and the liver and spleen were not palpable. No masses were palpable. Vaginal examination was normal.

Several routine urinalyses were normal. A complete blood count revealed a hemoglobin of 13.2 gm./100 ml., with a white cell count of 14,000, with 71% segmented, 25% lymphocytes, 2% eosinophils and 1% basophils. Sedimentation rate was 29 mm./hour. Hematocrit was 41%, and the fragility test was normal. Heterophil antibodies were not increased. Fasting blood sugar was 78 mg.%; urea nitrogen, 15 mg.%; albumin, 3.5 gm.%, globulin, 3.7 gm.%. Icterus index, cholesterol, cephalin flocculation and alkaline phosphatase were within normal limits. Two L.E. preparations were negative. X-ray examination of the chest and flat plate of the abdomen revealed no abnormalities. Electrocardiogram revealed that over the left precordium the T waves were low, flat or inverted. Culdoscopy revealed normal appearance of the pelvic organs, with no indication of the presence of endometriosis. No abnormality was noted to explain the repetitive nature of the episodes of peritonitis. Attacks have continued unabated since then, still having their fixed association with the menstrual period.

Comment

Certain characteristics have been noted in the group of patients suffering from the disorder of recurrent peritonitis which seem to distinguish it from the other repetitive diseases. Whereas periodic disease generally has shown no special predilection for any racial group, bouts of abdominal pains have been noted almost exclusively in individuals of Jewish, Arabic and Armenian extraction.

Reimann et al.[10] investigated the ethnic distribution of the disease in Lebanon, where the make-up of the population offers an unusual opportunity for study of this problem. Within five years, 72 cases were collected—49 in Armenians and 23 in Arabs. The hereditary and familial aspect of the disorder is also significant, since it appeared in members of the same family and in descendants of some of the sufferers—in one instance, 20 individuals in five generations were afflicted.

Similar observations were made by Heller et al.[11] who added 74 cases of their own to 174 collected from the literature. They emphasized the unusual preponderance of individuals with Jewish, Arabic and Armenian background among their patients and, in addition, reported a familial incidence of 60%. These authors also observed a distinction in prognosis. The ultimate outcome in most other forms of periodic disease is good, since complete recovery ensues after each attack, and although relapses may appear for years, the general health of the patient apparently is not compromised. This benign prognosis may not always be present in patients with periodic peritonitis, since renal complications have been observed ranging from proteinuria to renal failure and nephrosis due to amyloidosis and uremia. In this connection, the report[12] of a case of this disease that manifested hematuria simultaneously with the acute attack of abdominal pain is of interest. Because of these special features, the authors have suggested recently that this group forms a special entity which should be separated from the more general classification of "periodic disease," and have proposed "familial Mediterranean fever" as a more appropriate name. This has been defined as heredo-familial syndrome of undetermined pathogenesis in persons of Mediterranean stock becoming manifest as a rule in infancy and adolescence, and characterized by short recurrent bouts of fever, accompanied by pain

in the abdomen or chest or one or two multiple joints, singly or in various combinations." Although the pathogenesis is unknown, the authors suggest the possibility of an inborn error, either biochemical or structural, as the basic defect. Further observation and investigation will be necessary to determine the exact position of the syndrome in relation to periodic disease.

The underlying mechanism which precipitates the symptoms of the cyclic disease is still unknown. There has been no reported instance of association of periodic disease with the menstrual cycle, as occurred in the patient studied. In this patient there was no observed abnormality in the genital tract, such as endometriosis, which may have caused difficulty during the menses. This opinion was expressed by the gynecologists who examined her, and was based on the clinical picture of the attack, physical examination, and normal culdoscopic appearance of the pelvis. Although the menstrual cycle has been accompanied by allergic phenomena [13] and by certain disturbances such as edema, purpura and neutropenia,[14] the clinical picture of this patient has never included these features. The acute attack has always been typical of recurrent peritonitis, with the additional factor of occurrence only at the menstrual period. One puzzling aspect of the situation is immunity from abdominal pain during one menstrual period and susceptibility in another, with no other apparent differences between the two periods.

Paroxysmal peritonitis has been described in children,[15] in women past the menopause, and in men, so that it seems difficult to incriminate any fluctuation in a hormonal cycle as the inciting cause. Certain associations have been observed, however, which may have some significance. Most of the reported cases of recurrent peritonitis have had a cessation of attacks during pregnancy. The peculiar relations of pregnancy in general and menstruation in particular in this case would suggest that in this patient, at least, endocrine variation may play an important role.

Summary

Attacks of recurrent peritonitis occurred for years in a young Jewish female. An unusual feature was the appearance of each attack only in association with a menstrual period, a relationship apparently not before noted.

The significance of hormonal influences as a factor in the production of attacks is discussed.

Addendum

Since this paper was submitted for publication, the following events occurred. There was complete stoppage of all attacks during a pregnancy. After delivery, there was a resumption of the typical episodes of abdominal pain again associated with the menstrual periods. An exploratory laparotomy was performed at the height of a typical bout but no pathologic changes were found in the abdomen to explain the recurrent appearance of symptoms. Biopsy of the peritoneum revealed marked leukocytic infiltration.

Summario in Interlingua

Morbo periodic comprende un gruppo de disordines que se manifesta in recurrente attaccos a intervallos regular o irregular, con—apparentemente—complete restablimento inter le episodios. Le varie formas ha essite designate secundo lor plus eminente aspecto, e le principales ha essite listate como periodic abdominalgia (benigne peritonitis paroxysmal), periodic neutropenia, e periodic arthritis. Benigne peritonitis paroxysmal es specialmente importante a causa del difficultate de distinguer lo del acute abdomine chirurgic. Le tableau clinic es variemente componite del

elementos de algor, febre, nausea, vomito, e sever dolores e hyperesthesia in le abdomine. Le stadio acute ha un duration de inter duo e tres dies.

Le etiologia continua esser obscur. Le episodios pote recurrer a intervallos regular o irregular. On ha considerate los como independente del cyclo menstrual.

Es reportate le caso de un feminina judee de provenientia syriac qui experientiava repetite attaccos de sever dolores abdominal associate con algor, febre, e hyperesthesia abdominal, occurrente solmente durante le cyclo menstrual. Un alleviamento de omne le mentionate manifestationes occurreva durante le curso de un pregnantia. Postea le attaccos deveniva plus frequente.

Le examine durante un intervallo exempte de symptomas revelava nulle causa pro le repetite episodios. Un apparentia normal del organos pelvic esseva notate in le studio culdoscopic, sin ulle indication de endometriosis. Esseva concludite que le recurrente attaccos esseva un manifestation de morbo periodic.

Certe characteristicas ha essite notate in le gruppo de patientes qui suffre ab le disordine de peritonitis recurrente, distinguente lo ab le altere morbos repetitive. Peritonitis recurrente ha essite constatate quasi exclusivemente in subjectos de extraction judee, arabe, o armenie e in membros del mesme familia o in le descendentes de afficitos. Le prognose es minus benigne que in le altere manifestationes de morbo periodic, proque complicationes renal del typo de proteinuria, nephrosis, amyloidosis, e uremia occurre ultimemente in un certe numero de iste individuos. Le condition ha essite notate in ambe sexos.

In le majoritate del casos de peritonitis recurrente in feminas, le attaccos cessa durante pregnantias. In plus, le patiente del presente reporto habeva manifestationes del morbo solmente durante le menses. Isto justifica le these que fluctuationes endocrin ha un rolo importante in de precipitation del acute episodios.

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EDITORIAL

EXCLUSION OF PATERNITY *

THE National Office of Vital Statistics [1] estimated that there were more than 200,000 illegitimate births in the United States in 1957. A comparison of this figure with estimates for previous years demonstrates that the illegitimacy rate has more than doubled in the last 15 years. The problem is a serious one, and if the trend continues the problem will become much more serious. Of the 200,000 illegitimate births more than 50% were to mothers 17 years old or younger.

In an attempt to rectify some of the inequities created by the birth of children out of wedlock, it is necessary to establish the responsibility of the fathers of these children whenever possible. An accusation of paternity is a serious charge, which may have effects far beyond the merely momentary inconvenience of support for a child. Because such charges are easy to make but difficult to disprove, the rights of an accused man must be protected by court action. The court must of necessity take into account the interests of the child, his mother, the putative father, and of society. Many welfare agencies require that an unwed mother institute proceedings against some man as a prerequisite of eligibility for assistance. There is much justice behind this attitude, for if a man can be determined to be the father of a child, he, and not the taxpayer, becomes responsible for the support of that child. Unfortunately, such cases frequently result in tangled webs that are not easily resolved. It is for this reason that many responsible officers of the courts and welfare workers have welcomed the development of paternity exclusion technics based on serologic methods as aids in making some of the necessary decisions.[2-5a]

Unfortunately, the majority of men involved in paternity suits do not contest the charge. Sussman and Schatkin [6] reported recently on this phase of the problem. They invited men and women who were involved in litiga-

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[1] Vital Statistics of the United States, 1957, Vol. 1, U. S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics, 1959, U. S. Government Printing Office, Washington, D. C., p. 84.

[2] Use of paternity tests in criminal proceedings for nonsupport, J. A. M. A. **165**: 2204, 1957.

[3] Schatkin, S. B.: Disputed paternity proceedings, 3d Ed., 1953, Matthew Bender & Company, Inc., Albany, N. Y.

[4] Schatkin, S. B., as told to Smith, R. L.: The scandal of our paternity courts, Reader's Digest **76**: 71–76 (May) 1960.

[5] Wiener, A. S., Owen, R. D., Stormont, C., and Wexler, I. B.: Medicolegal applications of blood-grouping tests, J. A. M. A. **161**: 233–239, 1956.

[5a] Wiener, A. S., Owen, R. D., Stormont, C., and Wexler, B.: Medicolegal applications of blood-grouping tests, J. A. M. A. **164**: 2036–2044, 1957.

[6] Sussman, L. N., and Schatkin, S. B.: Blood-grouping tests in undisputed paternity proceedings, J. A. M. A. **164**: 249–250, 1957.

tion relating to paternity to submit to blood-grouping tests after the case had been settled by the defendants' admission of paternity; coöperation was obtained in 67 cases. Three children were found by the ABO system not to be the offspring of the putative father. Similarly, the M-N and Rh-Hr systems excluded three and two children, respectively. Admission of paternity is obviously unreliable, and it is urged in the interests of justice that a blood test be ordered in every case involving a charge of paternity. The factor responsible for admission of paternity usually is one of these: (1) a sincere belief that he is the father, (2) a sense of pride that he could be the father, (3) a total lack of financial responsibility, (4) inability to afford defense of the action, or (5) ignorance.

There is a great volume of literature relating to paternity testing. Some of the best of this are the books of Schatkin [3] and of Wiener and Wexler,[7] and Race and Sanger's textbook [8] which, while more general, has several excellent chapters relating to this subject.

Studies for the exclusion of paternity are merely applications of genetic principles to relatively easily measured and stable somatic characteristics. The presence or absence of various antigens is determined serologically. The inheritance of the blood group factors follows well-defined rules. When data obtained from such studies on the bloods of the child, the mother, and the putative father are analyzed, it is possible in many instances to exclude the man as the father of the child. The tests cannot show that a man is the father of the child. Although the data may show odds overwhelming enough to be convincing to the immunologist, it nevertheless is not acceptable even to make such a suggestion in court. Thus, the results can only exclude the possibility of paternity. The fact that the tests fail to exclude a man is not accepted as evidence that the man is the father of the child in question.[3, 7]

In Europe, where paternity exclusion studies are applied much more generally than in the United States, much work has been done which attempts to play percentages to calculate the probability of an individual's being the father of a child in instances in which paternity cannot be ruled out. Briefly, the technic consists of comparing the probability of one man's being the father with that of the "random man." In one case, two suspects were considered. The probability that the first man was the father was determined to be 1:518; however, the other man's probability was 226:1 in favor of his being the father.[9] For better or for worse, the American courts have not accepted such evidence, but it must be admitted that the idea is intriguing to a person with a mathematical mind.

Sidney B. Schatkin, who is a former corporation counsel for the City

[7] Wiener, A. S., and Wexler, I. B.: Heredity of the blood groups, 1958, Grune and Stratton, New York.

[8] Race, R. R., and Sanger, R.: Blood groups in man, 3d Ed., 1959, Charles C Thomas, Publisher, Springfield, Ill., p. 122.

[9] Nijenhuis, L. E.: Probability of paternity in cases where exclusion by blood group test is not possible, Proceedings of the First International Congress on Human Genetics, Part 3, pp. 607–611, 1957.

of New York, has written extensively in this field. His book, *Disputed Paternity Proceedings,*[3] is a definitive treatise on the legal aspects of paternity testing. He states that the first blood test law was enacted in New York State in 1935 as part of the Domestic Relations Law, although previously some use had been made in the courts of New York and of other states of the principles of blood group genetics. The New York law requires that a blood test be done if it is requested by the defendant, and provides that the results of this test are admissible as evidence only if an exclusion is determined. Wisconsin passed a similar law a few months after the New York statute was enacted, and since then other states have either enacted statutes to ensure that such tests may be used or have court rulings that effectively set precedent for the ordering of such procedures. In our own experience, a case which was reviewed by a state supreme court was returned to a lower court for retrial because serologic studies had not been carried out. Subsequent studies carried out in my laboratory demonstrated a double exclusion, thus aiding to terminate a legal controversy which had gone on so long that the child whose paternity was questioned had to be given leave by the Navy in order to return home for the necessary blood tests.

At the present time, it is generally accepted and it is the recommendation of the Committee on Medicolegal Problems of the American Medical Association [5] that only the three best-known systems of blood grouping be used in paternity studies. Use of the ABO, M-N, and Rh-Hr systems gives a wrongly accused man better than a 50% chance of being cleared by one or more of the combined tests. The laws of inheritance pertaining to these systems have been worked out to the point where there is absolute certainty that exceptions do not occur. It is essential to check ABO grouping by doing reversed grouping in order to recognize weak forms of A or the Bombay type of blood. Studies on the dosage effect of the M-N antigens serve to eliminate the possibility that the M_g antigen is present to complicate the interpretation of the test for this system. Diagnostic sera are of course not available for the d antigen, and many of the variants in this system are not considered for technical reasons. Knowledge about the more recently discovered blood systems is in the stage of being "quite certain," but it is to the advantage of the technic to delay presenting such evidence in court until our information about them has passed into the "absolutely certain" classification.

Genetic Principles

The basis of blood grouping is built upon the original observation of Karl Landsteiner [10] in 1900 that when some human bloods were mixed with other human bloods the erythrocytes of one or both bloods were lysed or agglutinated. This observation was extended, and evolved into the im-

[10] Landsteiner, K.: Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blusterums und der Lymphe, Centralbl. f. Bakt. **27**: 357–362, 1900.

portant *ABO system* of blood groups, the knowledge of which has made blood transfusion therapy possible and which has vast application in studies in human genetics. The inheritance of the three antigens that are responsible for the division of human bloods into four groups was determined later to be brought about by means of three allelomorphic genes.[11, 12] As knowledge of subgroups of A developed, this theory was extended to include allels for each of the subgroups. The genes responsible for the A and B factors have equal dominance; when present in an individual, both are expressed in the phenotype so that the person possessing them has blood of group AB. However, both of these genes are dominant over the gene producing the O factor and so the genotype of a person with group A blood may be AA or AO. The O gene expresses itself only in the pure recessive individual, so that the person with group O blood is always genotypically OO. It is impossible to differentiate between heterozygous and homozygous persons with blood group A or B except by family studies. The practical application of these observations is obvious. A child cannot possess a gene that is not present in one or both of his parents; thus a child with blood group A cannot be the child of two persons with blood group O, or of a mating of persons with blood of groups B and O. Indeed, regardless of the blood group of the other parent, it is impossible for an adult with blood group AB to be the parent of a child with blood group O; conversely, an adult with blood group O cannot be the parent of a child with blood group AB. Utilizing the principles developed around the ABO system alone, about 20% of wrongly accused men can be excluded as fathers.

The M-N system was described by Landsteiner and Levine in 1927.[13] Disregarding very rare variants, two genes are involved in this system. They show no dominance over each other, so that the genotype is fully expressed in the phenotype. Three blood types are determined by the genes; blood types M, N, and MN have genotypes MM, NN, and MN, respectively. A child whose blood is of type M cannot have a father whose blood is of type N, for if he did inherit a gene from such a father he would have blood of type MN or NN. Other possibilities for exclusion work out rather easily, and about 18% of innocent men can be eliminated by this system. The recent addition of the S and s factors to this system complicate it, but extend its usefulness.

The Rh blood system was discovered nearly 20 years ago as the result of the work of Landsteiner and Wiener.[14] It has proved to be the most efficient single system used in exclusion studies to date. Many of the

[11] Bernstein, F.: Ergebnisse einer biostatistischen zusammenfassenden Betrachtung über die erblichen Blutstrukturen des Menschen, Klin. Wchnschr. **3**: 1495–1497, 1924.

[12] Race, R. R., and Sanger, R.: The inheritance of blood groups, Brit. M. Bull. **15**: 99–109, 1959.

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[14] Landsteiner, K., and Wiener, A. S.: An agglutinable factor in human blood recognized by immune sera for rhesus blood, Proc. Soc. Exper. Biol. and Med. **43**: 223, 1940.

antigens included in this system are relatively strong, and hence the diagnostic sera necessary for their detection are relatively easy to procure. The distribution of the antigens follows a pattern which makes for the most effective application of this technic. The Rh-Hr system, to use Wiener's terminology,[7, 14, 15] is composed of three pairs of factors and their variants. Fisher and Race [16] have designated the principal factors as C-c, D-d, and E-e, and these correspond to Wiener's rh′-hr′, Rh_o-Hr_o, and rh″-hr″. The two forms of nomenclature are based on two entirely different concepts of the inheritance of the blood factors. The Fisher-Race theory holds that these factors are produced as the result of the action of three pairs of allelomorphic genes that are closely linked and hence only rarely show crossing over. Wiener, on the other hand, maintains that there are eight allelomorphic genes. Regardless of which theory is correct, the inheritance patterns are the same and fit into both concepts, as the eight basic subtypes are readily explained by either theory. It is unfortunate that so much energy and time has been consumed in arguing over the relative merits and disadvantages of each system of nomenclature. As it appears that the opposing camps will not be reconciled in the near future, the immunologist who participates in paternity exclusion work can best avoid difficulties by using both systems in his report. Certainly, if he understands his work thoroughly, he knows both systems of nomenclature and understands their derivation and development.

Who Should Perform the Tests?

The decision as to who may be qualified as an expert for the purposes of carrying out these tests for the court is a serious one. When paternity exclusion studies were first introduced, it was recommended that only those who made and standardized their own diagnostic sera were competent to be considered as experts. Obviously, this is impractical today when commercial sera are so readily available and are so generally used. In New York State and in some other jurisdictions, only physicians may be appointed as experts,[3] but this has proved impractical elsewhere, as this rule excluded many competent persons available to do the tests.

The problem of defining an expert may become much more serious, for an increasing demand for this service will encourage persons to undertake the work who are obviously not competent to do it well. The medical technician who carries out the tests with the textbook propped open and the pathologist who is so far removed from the actual work of the laboratory that he is unable or unwilling to carry out these tests himself are both unsuitable candidates for the role of expert. Unfortunately, the courts are frequently not in a position to make an intelligent selection of experts unless they have help and advice from the medical community. This, then, be-

[15] Wiener, A. S., Unger, L. J., and Sacks, M. S.: Rh-Hr blood types—present status, J. A. M. A. 172: 1158–1162, 1960.

[16] Fisher and Race, cited by Race and Sanger.[12]

comes the responsibility of the medical profession. As a guide for lawyers and courts, the Law Department of the American Medical Association has clearly stated its criteria for qualified blood grouping specialists.[5] In many other instances, help in the selection of the proper persons as experts has been obtained from local organized medical groups.

Conduct of the Tests

The conduct of these determinations is not easy.[17] Special precautions must be taken to avoid errors in the identity of the individuals to be tested. For this reason, it is well to avoid specimens collected by others and mailed in. While fraud is a remote possibility, it may occur. The best method seems to be to bring the interested parties to the office at the same time. In this way, the adults can identify each other, and if the man knows the baby he can identify the child to his own and the examiner's satisfaction. Sometimes neither of the adults can identify the child; then identification may be made by the social worker assigned to the case. Permanent records should be made at the time of the interview to note scars, tattoos, or other distinguishing marks. Fingerprints or palm prints may be made but they are possibly of more value in impressing the persons involved in the case with the seriousness of the identification than in actual identification. One expert in this field takes pictures of his clients with a Polaroid Land camera and has the principals endorse the pictures by signing them on the back; these pictures become part of his permanent record.

Because people are often confused by the terminology of blood groups and either have forgotten or remembered incorrectly the results of previous blood grouping tests, it is always well to inquire whether or not any of these people know their blood groups. This then protects the expert if his determination disagrees with what the person believes his blood group or Rh type to be. The expert is in a position to say that he has reached his decision about the patient's group with the knowledge that another report had been given previously, and that it is his opinion that the previous report is in error. This makes a much more favorable impression on the witness stand than the situation in which the previous determination was unknown.

Duplicate specimens of blood are taken from each person involved in the case. It is usually possible to get venous blood from the children, but if it is not feasible to do this, capillary blood is satisfactory. All specimens are, of course, carefully labelled. One set of specimens is retained by the expert for his personal study, and the other set is sent to another part of the laboratory where independent analyses can be carried out by others. Whenever possible, these two workers should use antisera from different sources and different technics. All results are completed and recorded before a conference is held. Discrepancies, if any, are resolved by rechecking specimens

[17] Sussman, L. N.: Pitfalls of paternity blood grouping tests, Am. J. Clin. Path. 33: 406–415, 1960.

with different sera or methods, and sometimes by calling the contesting parties back for new specimens.

Great care must be taken to control the technics used in the test. Control specimens must be available, and must be used especially when dealing with the M-N, Duffy, and Kell systems. The blood specimens must be examined when they are as fresh as possible, even though properly stored specimens will give valid results when they are 10 or more days old. Every attempt must be made to conform with the directions recommended by the manufacturer of the serum, as in most instances these instructions yield the best results. Finally, a summary is prepared in triplicate for the court or for the defendant's lawyer. Telephoned reports are not made.

In reviewing the last 160 cases studied in our own laboratory, there were 22 exclusions. The bulk of these cases were referred from the Juvenile Court of Cuyahoga County, and were described as carefully screened cases. Our figure of 14% exclusions compares favorably with the 16% found by Marsters,[18] who reported 32 exclusions in 200 cases in 1957. To a large extent, his case material was referred to him by the same court, and came from the same type of population as ours did. Our series contains one triple exclusion and three double exclusions; the remainder are single exclusions.

Other Applications of the Test

Aside from the exclusion of paternity in cases involving children born out of wedlock, the principle has been applied to children born in wedlock in divorce and nonsupport cases.[2] Various other applications of the genetics of blood groups readily come to mind. The inheritance of blood group factors bears no relationship to the sex of the parent; hence it is quite possible that under special circumstances, maternity as well as paternity could be investigated. Identification of babies in cases of kidnapping or hospital nursery mix-ups could conceivably be accomplished by the application of these principles. Indeed, it might be possible to assist in the identification of a body, even if the individual's blood group had not been previously known, if enough of the individual's family were available for a family study. The immigration service may require blood tests on adults seeking derivative citizenship. This has principal application to Orientals who seek citizenship on the basis of having parents or other relatives who are citizens. Blood group determinations have increasing importance in genetic studies of familial diseases. In our own practice, a promising family study of a hemolytic disorder was cancelled after an almost accidental observation of a paternity exclusion based on the Rh-genotypes of the child and his parents. Blood antigens have much importance in evaluation of donors and recipients in tissue and organ grafts. The acceptance of the graft by the patients appears to be closely related to the degree of similarity of donor and patient

[18] Marsters, R. W.: Determination of nonpaternity by blood groups; a series of two hundred cases, J. Forensic Sc. **2**: 15–37, 1957.

blood group antigens. In the nonmedical field, many animal breeders and breed associations are applying the genetic principles of blood groups to identify individual animals; this serves to make pedigrees more accurate by detecting dishonest practices and honest mistakes of the breeders.

The Future

The future possibilities of these principles and technics are almost unlimited. As more blood antigen systems are discovered and the present ones developed more completely, the percentage of innocent men who can be excluded by the procedure will increase. Our present statistical exlusion rate of 52% is based on the three accepted systems. By adding tests for four other systems, for each of which diagnostic sera are readily available, the exclusion rate is raised to 62%.[19] Indeed, if blood grouping becomes more precise and includes an increasing number of factors, blood antigenic patterns will be as characteristic for the individual as fingerprints are today. Actually, it may be possible to *determine* paternity instead of merely being able to *exclude* it. Even at the present time, most workers in the field carry out determinations for subgroups of A, and for Kell, Duffy, and other factors, which have not been accepted generally by the courts but are, nevertheless, supplemental evidence of some value. But the time should come when such evidence will be based upon enough experience and experimental data to be as acceptable as the presently accepted ABO, M-N, and Rh-Hr systems. Other possibilities include the exploration of antigens present in platelets, leukocytes, and plasma. Even the types of hemoglobin may, in special instances, be useful information to have. The secretion phenomenon and the understanding of the ability to taste various phenylthiocarbamides have been developed to the point where they appear to be promising leads for the future.

John W. King, M.D., Ph.D.

[19] Boyd, W. C.: Chances of disproof of false claims of parent-child relationship, Am. J. Human Genet. **9**: 191–194, 1957.

REVIEWS

Clinical Endocrinology. I. Edited by E. B. Astwood, M.D. 724 pages; 23.5 × 15.5 cm. Grune & Stratton, Inc., New York, N. Y. 1960. Price, $18.75.

This book represents a follow-up of *Progress in Clinical Endocrinology* published in 1950. Sections are devoted to each endocrine gland and, in addition, there is a section on selected topics dealing with the relationship of hormones to fat, skin, cancer, red cell production and the kidney. The final section is devoted to methods of hormone assay, their significance and limitations. Each chapter is written by authors who are actively engaged in advancing knowledge in that particular subject.

The book consists largely of discussions of physiological mechanisms correlated with clinical disease entities. It is not the purpose to provide complete coverage of well-established clinical disorders and there are no didactic presentations of the diagnosis and treatment of such diseases as myxedema and diabetes mellitus. For the most part, topics in which knowledge is limited and controversial points of view are involved are presented comprehensively. However, bias in favor of a particular author's own opinion inevitably arises; this is noticeable in the chapters on discussions of thyroid cancer where treatment by total thyroidectomy followed by radioiodine is given little deserving consideration.

This book is an excellent treatise for students and physicians with special interests in endocrinology. It should be valuable also as a reference for practicing physicians who desire to obtain a better understanding of a particular clinical problem. The field of endocrinology is expanding so rapidly that it is pertinent for books like this one to be published periodically.

J. G. W.

The Physiological Basis of Diuretic Therapy. (Publication Number 366, American Lecture Series. A Monograph in the Bannerstone Division of American Lectures in Physiology.) By Robert F. Pitts, Ph.D., M.D. 332 pages; 24 × 15.5 cm. Charles C Thomas, Publisher, Springfield, Illinois. 1959. Price, $9.75.

During the last 10 years diuretic agents have become of paramount importance in clinical medicine. The widespread use of these agents has placed an increasing burden of responsibility on the physician regarding the proper choice, natural history and complications of diuretic therapy. To provide the best service to his patient when using a diuretic agent, the physician must now substitute rational therapy for his previous empirical choices. Urgently needed has been information under one cover concerning the fundamentals of renal physiology, the pathophysiology of edema and the mechanisms of diuretic agents. Dr. Pitts, who needs no introduction to students of renal physiology, has performed an outstanding service in writing this monograph concerning the mechanism of edema formation and the modes of action of diuretics. Indeed, there is much more here than indicated by the title. Concise and unusually clear discussions of renal and body fluid physiology, of the anatomy and function of the glomerulus, and of the volume regulatory mechanism for extracellular fluids distinguish this book from the usual discussion of diuretic therapy.

Dr. Pitts' book is divided into two parts: Part I presents basic information concerning fluid balance and the abnormalities of function which result in the formation of edema. Renal physiology receives unusually lucid treatment. To this reviewer's knowledge this is the first major text to present the counter current theory as the most plausible method responsible for the formation of dilute and concentrated urine.

The presentation is made comprehensible by Dr. Pitts' distinction between the counter current exchange mechanism of the renal capillary loops and the counter current multiplication of concentration in the loops of Henle.

Part II begins with Dr. Pitts' familiar functional classification of diuretics and continues with a discussion of the mechanism of action, dosage and toxicity of these with practical clinical application. The spirolactones, osmotic diuretics and sulfonamyls receive attention with emphasis on their contributions to understanding renal physiology.

This well written monograph clearly defines our current state of knowledge regarding renal tubular handling of salt and water. It should be required reading for those responsible for patient care. It will be of outstanding value to students of renal physiology. All readers will find this manuscript delightful medical reading.

FRANCIS J. BORGES, M.D.

Early Diagnosis. Edited by HENRY MILLER, M.D., F.R.C.P. 400 pages; 22.5 × 14 cm. The Williams and Wilkins Co., Baltimore. 1959. Price, $6.50.

This small volume is a collection of short essays on diagnosis and differential diagnosis by 25 contributors. Almost all contributors are specialist physicians practicing in Great Britain, the majority in London. Each contributor has presented one chapter on the early diagnosis of one particular problem such as the acute abdomen, coma, liver disease, skin disease, etc. The subjects are dealt with in a most general fashion which limits sharply the value of the presentation. It is this reader's opinion that the outstanding chapter is the first, entitled "On Early Diagnosis," by Lord Cohen of Birkenhead, Professor of Medicine at the University of Liverpool. This chapter presents an extremely practical approach toward diagnosis of disease. It also presents nine invaluable aphorisms on diagnosis which all physicians should constantly keep in mind.

It is difficult to determine the role which this book should play. Although in the preface the editor states that it was prepared for the use of the general practitioner, it is doubtful if any general practitioner would gain much from reading the volume, which he cannot readily obtain in the books already in his library. The same objection can be made for its use by the medical student. The volume is not useful as a reference volume nor as a helpful manual for the busy physician.

C. V. B.

Arterial Embolism in the Limbs: The Clinical Problem and Its Anatomical Basis. By A. L. JACOBS, M.A., D.M. (Oxon.), F.R.C.P.; foreword by C. G. ROB, M.C., M.A., M.Chir. (Cantab.), F.R.C.S. 200 pages; 25.5 × 17.5 cm. The Williams & Wilkins Co., Baltimore. 1959. Price, $8.00.

This is a concise and comprehensive review of the problem of peripheral arterial embolism. The study is based on collected clinical and morbid anatomical material observed by the author at three general hospitals in London.

A brief and satisfactory historical note prefaces the clinical material presented. There is an invaluable section devoted to anatomical variations in arterial collaterals. Fifty-seven adult cadavers injected with Hauch's fluid were used for this phase of the study. Diagnosis and postmortem arteriograms are clear and liberally presented.

The incidence of limb embolism in mitral stenosis is analyzed as well as the aspects of general etiology. An excellent section is devoted to morbid anatomy. Clinical features, diagnosis, prognosis, and therapy are well discussed. The role, if any, of arterial spasm is clarified from the author's viewpoint. A summary of main conclusions is an excellent guide to this difficult problem.

There is an appendix containing excellent illustrative case reports. The indexing is comprehensive and the cross indexing thoroughly adequate.

GEORGE H. YEAGER, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Bibliography on Bilharziasis, 1949–1958. 158 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $2.00.

A Clinical and Genetico-statistical Study of Schizophrenia and Low-grade Mental Deficiency in a Large Swedish Rural Population. Acta Psychiatrica et Neurologica Scandinavica *Supplementum 140, Volumen 35, 1959.* (From the Department of Psychiatry (Head: PROFESSOR TORSTEN SJÖGREN, M.D.), Karolinska Institutet, Medical School, Stockholm, Sweden.) By BERTIL HALLGREN and TORSTEN SJÖGREN. 65 pages; 24 × 16 cm. (paper-bound). 1959. Ejnar Munksgaard, Copenhagen. Price, kr. 33.75.

Conference on the Comparative Pathology of Arthritis and Rheumatism, Sponsored by the American Rheumatism Association, the Arthritis and Rheumatism Foundation and the National Institute of Arthritis and Metabolic Diseases at the National Institutes of Health, Bethesda, Maryland, February 5 and 6, 1959. (Reprinted from Laboratory Investigation, *Volume 8, Number 6, November-December, 1959.)* Conference Planning Committee: LEON SOKOLOFF, Chairman; WILLIAM S. CLARK, RONALD W. LAMONT-HAVERS, WILLIAM D. ROBINSON, JOHN H. RUST and CONRAD L. PIRANI. 350 pages; 26 × 18 cm. 1959. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.00.

Differentialdiagnose Innerer Krankheiten. By DR. ROBERT HEGGLIN. 913 pages; 24.5 × 17.5 cm. 1960. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 79.50.

Edema: Mechanisms and Management. A Hahnemann Symposium on Salt and Water Retention. Edited by JOHN H. MOYER, M.D., Professor and Chairman of the Department of Medicine, Hahnemann Medical College and Hospital; and MORTON FUCHS, M.D., Assistant Professor of Medicine, Hahnemann Medical College and Hospital. 833 pages; 25.5 × 16.5 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $15.00.

Electrocardiographic Techniques: A Manual for Physicians, Nurses and Technicians. 2nd Ed. By KURT SCHNITZER, M.D. 109 pages; 23 × 15 cm. 1960. Grune & Stratton, New York. Price, $4.75.

Expert Committee on Biological Standardization: Thirteenth Report. World Health Organization Technical Report Series No. 187. 49 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Fundamentals of Clinical Hematology. By BYRD S. LEAVELL, M.D., Professor of Internal Medicine, Physician-in-charge, Hematology Section, School of Medicine, University of Virginia, etc.; and OSCAR A. THORUP, JR., M.D., Associate Professor of Internal Medicine, School of Medicine, University of Virginia, etc. 503 pages; 25.5 × 16.5 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $10.00.

Guide to Hygiene and Sanitation in Aviation. Prepared by a WHO EXPERT COMMITTEE ON HYGIENE AND SANITATION IN AVIATION. 51 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Highlights of Progress in Mental Health Research, 1959: Items of Interest on Program Developments and Research Studies Conducted and Supported by the National Institute of Mental Health. Public Health Service Publication No. 736. Prepared by the PUBLICATIONS AND REPORTS SECTION, NIMH, JANUARY 1960. 51 pages; 23 × 14.5 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 25¢.

Insecticide Resistance and Vector Control: Tenth Report of the Expert Committee on Insecticides. World Health Organization Technical Report Series No. 191. 98 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. through Columbia University Press, International available in U. S. A. from Columbia University Press, International Documents

Local Health Service: Third Report of the Expert Committee on Public Health Administration. World Health Organizaiton Technical Report Series No. 194. 49 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

The Lymphocyte and Lymphocytic Tissue. International Academy of Pathology Monograph. (Series Editor: ROBERT E. STOWELL, M.D., Ph.D.) By 21 AUTHORS; edited by JOHN W. REBUCK, M.D., Ph.D., Chief, Division of Laboratory Hematology, Henry Ford Hospital, Detroit. 312 pages; 26 × 17.5 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York. Price, $10.50.

Medical, Surgical, and Gynecological Complications of Pregnancy. By THE STAFF OF THE MOUNT SINAI HOSPITAL, NEW YORK CITY; edited by ALAN F. GUTTMACHER, M.D., Obstetrician and Gynecologist-in-Chief, The Mount Sinai Hospital, New York; and JOSEPH J. ROVINSK, M.D., Assistant Attending Obstetrician and Gynecologist, The Mount Sinai Hospital, New York. 619 pages; 26 × 17.5 cm. 1960. The Williams & Wilkins Company, Baltimore. Price, $16.50.

Opere Alese. Vol. I: *Neurologie.* By C. I. PARHON. 374 pages; 24.5 × 18 cm. 1954. Editura Academiei Republicii Populare Romine, Bucharest.

Opere Alese. Vol. II: *Psihologie si Psihiatrie.* By C. I. PARHON. 527 pages; 24.5 × 17.5 cm. 1957. Editura Academiei Republicii Populare Romine, Bucharest.

Opere Alese. Vol. III: *Endocrinologie Generala, Glanda Tiroida, Glandele Paratiroide si Timus.* By C. I. PARHON. 583 pages; 24.5 × 17.5 cm. 1959. Editura Academiei Republicii Populare Romine, Bucharest.

Pathogenesis and Treatment of Occlusive Arterial Disease: The Proceedings of a Conference held in London at the Royal College of Physicians of London, 13th–14th November 1959. Edited by LAWSON MCDONALD. 237 pages; 23 × 15 cm. (paper-bound). 1960. J. B. Lippincott Company, Philadelphia. Price, $5.00.

A Primer of Electrocardiography. 4th Ed. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc.; and TRAVIS WINSOR, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California Medical School, etc. 293 pages; 24 × 16 cm. 1960. Lea & Febiger, Philadelphia. Price, $5.00.

Radioisotope Studies of Fatty Acid Metabolism. (Volume I of Division VI: *Medicine, International Series of Monographs on Nuclear Energy;* General Editors: R. A. CHARPIE and J. V. DUNWORTH.) By JAMES F. MEAD and DAVID R. HOWTON, Department and Laboratories of Nuclear Medicine and Radiation Biology, University of California, Los Angeles. 141 pages; 22 × 14.5 cm. 1960. Pergamon Press, Inc., New York. Price, $7.50.

Sex Differentiation and Development: Proceedings of a Symposium Held at the Royal Society of Medicine, Wimpole Street, London, on 10 and 11 April 1958. Memoirs of the Society for Endocrinology No. 7. Edited on behalf of the Society for Endocrinology by C. R. AUSTIN. 198 pages; 25.5 × 19 cm. 1960. Cambridge University Press, New York. Price, $8.50.

Surgery and Clinical Pathology in the Tropics. By CHARLES BOWESMAN, O.B.E., B.A., M.D., F.R.C.S.E., F.A.C.S., D.T.M. & H.Ed., Fellow of the Royal Society of Medicine, etc. 1,068 pages; 25.5 × 18 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, $22.50.

A Symposium on pH and Blood Gas Measurement: Methods and Interpretation. Edited by RONALD F. WOOLMER, V.R.D., B.A., B.M., F.F.A.R.C.S., Professor of Anaesthetics in the Royal College of Surgeons of England; assisted by JOY PARKINSON, B.A. 210 pages; 22.5 × 14 cm. 1959. Little, Brown and Company, Boston. Price, $8.50.

Types of Injuries: Incidence and Associated Disability, United States, July 1958–June 1959. Statistics on the Number of Injuries and Days of Disability Due to Injuries by Type of Injury, Class of Accident, Sex, and Age. Based on Data Collected in Household Interviews During the Period July 1958–June 1959. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584-B16. 36 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30¢.

MEDICAL NEWS

Postgraduate Education

The following Postgraduate Courses, under the auspices of the American College of Physicians, have been planned for Fall-Winter, 1960–61:

September 19–23, 1960	Hematology and Radioisotopes, Dr. Charles A. Doan, Director, The Ohio State University, Columbus, Ohio.
October 10–14, 1960	Cancer and the Internist—1960 Concepts, Dr. Rulon W. Rawson, Director, Memorial Sloan-Kettering Cancer Center, New York, N. Y.
November 7–11, 1960	Electrocardiography, Dr. Hans H. Hecht, Director, University of Utah College of Medicine, Salt Lake City, Utah.
December, 1960 (date not set)	Recent Advances in Pharmacotherapy, Dr. Robert H. Williams, Director, University of Washington School of Medicine, Seattle, Wash.
January 16–20, 1961	General Medicine, Dr. Stanley E. Bradley, Director, Columbia-Presbyterian Medical Center, New York, N. Y.
February 20–24, 1961	Selected Topics in Internal Medicine, Dr. Stewart Wolfe, Director, University of Oklahoma Medical Center, Oklahoma City, Okla.

For registration blanks and other information, contact Dr. Edward C. Rosenow, Jr., Executive Director, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

University of Washington School of Medicine announces a postgraduate course on anemias, September 15–17: Erythrokinetics, hemoglobinopathies, metabolic and isotopic technics. The staff will include Dr. Arno G. Motulsky, Dr. Robert S. Evans, Dr. Victor Herbert, Dr. Lester D. Ellerbrook, Dr. Eloise R. Giblett, Dr. Clement A. Finch and others. Inquiries may be addressed to:

Mrs. Marjorie Peters
Office of Postgraduate Medical Education
University of Washington
Seattle 5, Washington

The Thirteenth Annual Symposium on Pulmonary Diseases will be held at Fitzsimons General Hospital, Denver, Colorado, September 19–23, 1960. This Symposium is co-sponsored by the American Trudeau Society, the University of Colorado School of Medicine and Fitzsimons General Hospital. Tuition fee is $5.00. Information concerning enrollment may be obtained from the University of Colorado Medical School or from the Program Director, Colonel James A. Wier, Fitzsimons General Hospital, Denver 30, Colorado.

New York University Postgraduate Medical School announces a postgraduate course in gynecological endocrinology. "A practical, didactic and clinical presentation with emphasis on the therapeutic management of endocrine disorders in the female, including a discussion of the diagnosis and management of intersex will be offered. Endocrine therapy for menstrual abnormalities and ovulatory defects will be presented. Adrenocortical, thyroid, ovarian and pituitary abnormalities will be emphasized. Practical diagnostic tests are discussed and demonstrated, as well as the therapeutic use of the newer progestational, gonadal and corticoid steroids. Some pertinent aspects of male endocrinology will be included."

Five-day, full-time course, October 17 through October 21, 1960. Tuition: $140.00.

Given under the direction of Dr. Herbert S. Kupperman. For further information address: Office of the Associate Dean, New York University Postgraduate Medical School, 550 First Avenue, New York 16, N. Y.

Fellowships

Lemuel Shattuck Hospital, in coöperation with Warren Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University at Massachusetts General Hospital, has established a chemotherapy fellowship. The program will provide training in the use and critical evaluation of new chemotherapeutic agents in man and animals. There will be opportunity for individual research. Fellows should have prior training in internal medicine. For information contact Oncology Division, Medical Services, Lemuel Shattuck Hospital, Boston 30, Mass.

The Department of Pediatrics, New York University-Bellevue Medical Center, College of Medicine, has announced a fellowship available in pediatric allergy. The fellow will participate in current research activities and attend clinical sessions at Bellevue and University Hospitals. Applicants should have a minimum of two years in pediatrics. Salary will be $4,500 to $5,000. For information contact Vincent J. Fontana, M.D., NYU-Bellevue Medical Center, 550 First Avenue, New York 16, N. Y.

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1961, as follows: (1) *Until October 15, 1960,* for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend $4,500, with allowances for dependents and necessary travel. (2) *Until November 1, 1960,* for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

The Memorial Center for Cancer and Allied Diseases of Cornell University Medical College offers special fellowship for study in medical neoplasia. Candidates must be graduates of A.M.A. approved medical schools and must have completed or be in the process of completing two years of postgraduate training in internal medicine in addition to one year of internship. The salary stipend is $6,000 per year without

maintenance. It is for one year, renewable for two. For information contact Dr. Henry D. Diamond, Chief, Lymphoma Service, Department of Medicine, Memorial Center of Cancer and Allied Diseases, 444 E. 68th St., New York 21, N. Y.

The City of Hope Medical Center has announced a Fellowship in pediatrics. Time will be divided equally between clinical work (primarily leukemia and clinical genetics) and laboratory work (hematology, cytology, tissue culture, biochemistry). Applicants should be Board-qualified pediatricians eligible for California licensure. The fellowship will be for one to two years at a salary of $8,000 per year and will begin this year. For information contact Dr. Alfred G. Knudson, Jr., Department of Pediatrics, City of Hope Medical Center, Duarte, Calif.

Future Meetings

Sept. 1–3	International Congress of Nephrology. Evian, France, and Geneva, Switzerland. Secretariat: Prof. G. Richet, Hospital Necker 149, rue de Sevres, Paris 15e, France.
Sept. 5–9	2nd International Congress of Bioclimatology and Biometeorology. London, England. Secretariat: Dr. Solco W. Tromp, International Society of Bioclimatology and Biometeorology, Hofbrouckerlaan '54, Oegstgeest (Leiden), Netherlands.
Sept. 7–10	Meeting of Medical Women's International Association. Baden-Baden, Germany. Secretariat: Dr. Vera Peterson, 29, route de Malagnou, Geneva, Switzerland.
Sept. 16–22	14th World Medical Association. Berlin, Germany. Secretariat: Dr. Louis H. Bauer, 10 Columbus Circle, New York 19, N. Y.
Sept. 18–25	3rd European Congress of Cardiology. Rome, Italy. Secretariat: Dr. V. Puddu, c/o Clinica Medica Universita-Policlinico, Rome, Italy.
Oct. 17–21	Bockus Alumni International Society of Gastroenterology in Rio de Janeiro, Brazil. For information contact Dr. Figueiredo Mendes, Av. Rio Branco, 257–18, Rio de Janeiro, Brazil, or Dr. James L. D. Roth, Graduate Hospital, Rm. 520, Philadelphia 46, Pa.
Nov. 1–2	Association of Military Surgeons of the U. S. at Washington, D. C. Headquarters: Mayflower Hotel. General Chairman: Rear Adm. Curtiss W. Schantz, DC, U. S. Navy, Asst. Chief of Bureau of Medicine & Surgery for Dentistry, Navy Department, Washington 25, D. C.

Examinations and Licensure

Oct. 20–22	American Board of Pathology, at the Indiana University Medical Center, Indianapolis, Indiana. Final date for filing an application is September 15, 1960. For information contact Edward B. Smith, M.D., Secretary, Indiana University Medical Center, 1100 W. Michigan Street, Indianapolis 7, Indiana.

SPECIAL ANNOUNCEMENT

PAPERS FOR FORTY-SECOND ANNUAL SESSION

May 8–12, 1961, Miami Beach, Bal Harbour, Florida

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References:

1. Segal, M. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema, New York, Grune & Stratton, 1953. p. 99. 2. Farber, S. N., and Wilson, R. H. L.: Ann. Int. Med. 50:1241, 1959. 3. Barach, A. L., and Cromwell, H. A.: Med. Clin. No. America, May 1940, p. 621. 4. Bickerman, H. A., and Barach, A. L.: Drugs of Choice, 1960-1961 (W. Modell, ed.). St. Louis, The C. V. Mosby Co., 1960, p. 524.

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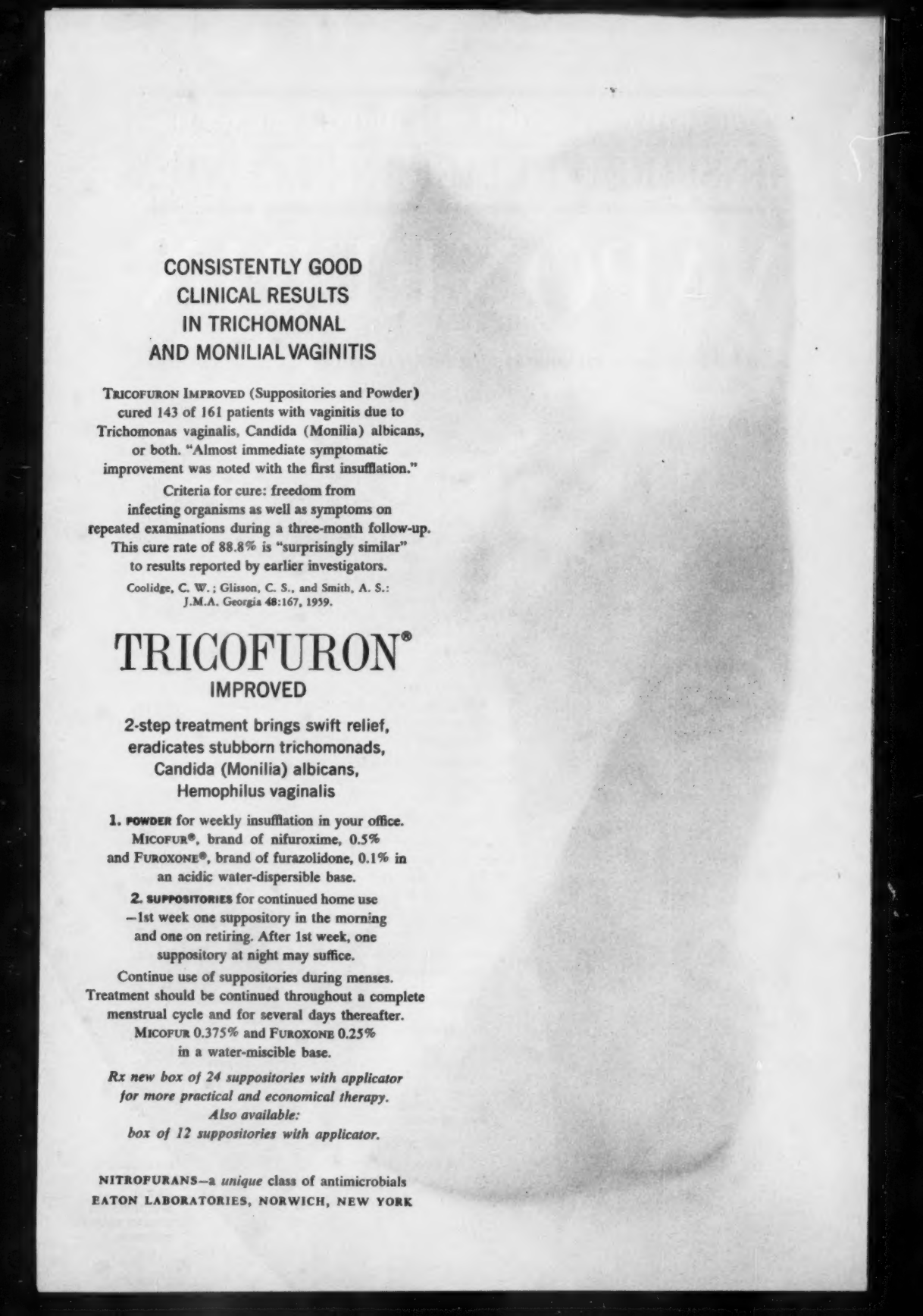

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BUTISOL has been shown[1] to be more effective with fewer side effects than other agents commonly used to control everyday nervousness, apprehension, tenseness and anxiety.

TABLETS · REPEAT-ACTION TABLETS · ELIXIR · CAPSULES

McNEIL McNEIL LABORATORIES, INC., Philadelphia 32, Pa.

1. Batterman, R. C.; Grossman, A. J.; Mourtoff, G. J., and Leifer, P.: A Clinical Re-evaluation of Daytime Sedatives, Scientific Exhibit, Annual AMA Meeting, San Francisco, Cal., June 23-27, 1958.

Controls compulsive overeating

CURBS APPETITE... RELIEVES TENSION HUNGER... TRANQUILIZES "DIET JITTERS"

Why do so many overweight patients so often break their diets?

The reason is usually tension.[1,2,3] Now—Appetrol has been formulated to help you solve this problem.

Appetrol provides dextro-amphetamine to curb your patient's appetite. Even more important, it provides meprobamate to control compulsive overeating, to ease the frustration of the dietary regimen—and to minimize the jittery effects of amphetamine.

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References: 1. Freed, S. C.: Psychic factors in the development and treatment of obesity. J.A.M.A. *133*:369, Feb. 8, 1947. 2. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, Oct. 1958. 3. Plotz, M.: Modern management of obesity—the "social diet." J.A.M.A. *170*:1513, July 25, 1959.

Usual dosage: 1 or 2 tablets one-half to 1 hour before meals. Each tablet contains: 5 mg. dextro-amphetamine sulfate and 400 mg. meprobamate.

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ACTS FASTER—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients.

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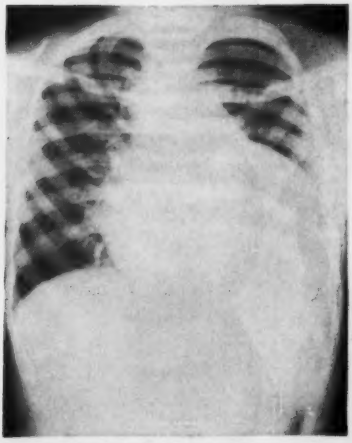
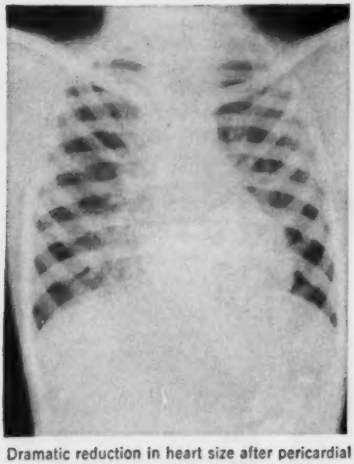


Pericarditis with pericardial effusion; roentgenogram before therapy.



Dramatic reduction in heart size after pericardial tap of only 150 cc. and 6 days of Medrol therapy.

X-rays courtesy of Lorin E. Ainger, M.D.

In 243 patients hospitalized for acute rheumatic fever, *high-dosage corticotherapy* led to regression or disappearance of significant murmurs at least twice as often as did management with salicylate, small doses of steroid, or no medication. *Early initiation of therapy* increased the percentage of patients showing cardiac improvement.[1]

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Medrol*

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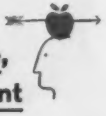
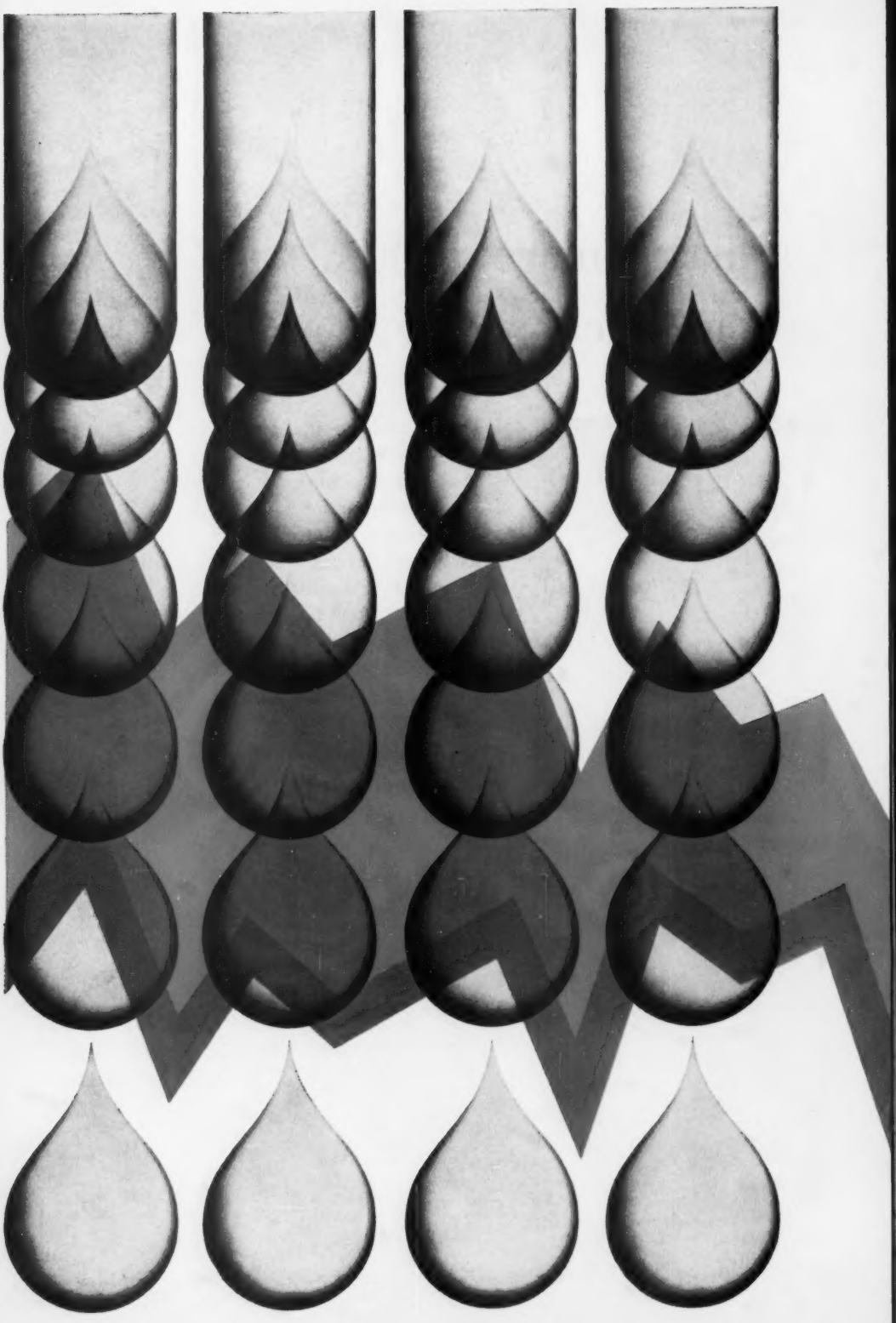
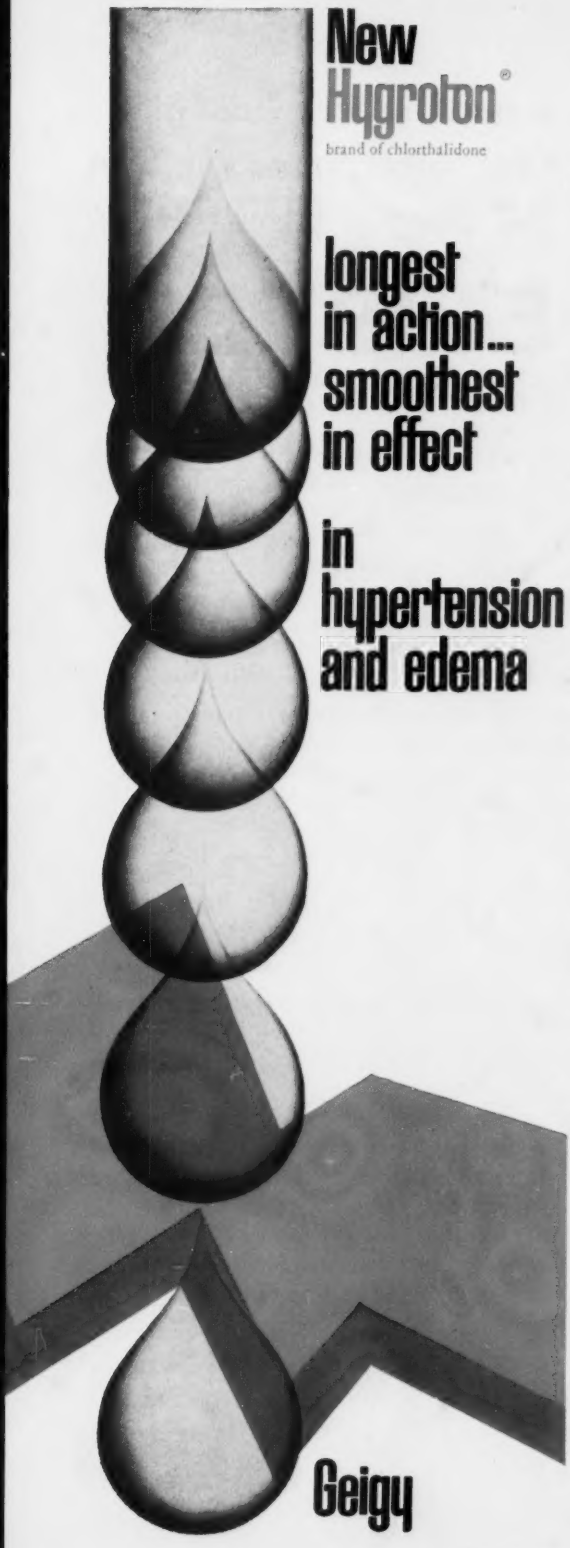


Supplied: As 4 mg. tablets in bottles of 30, 100 and 500; as 2 mg. tablets in bottles of 30 and 100; and as 16 mg. tablets in bottles of 50.

*TRADEMARK, REG. U. S. PAT. OFF.—METHYLPREDNISOLONE, UPJOHN

1. Massell, B. F.: Paper presented at A Symposium on Steroid Therapy, Chicago, Ill., May 15-16, 1959.





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lesser loss of potassium

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More detailed information available on request.

Bibliography
1. Stenger, E. G. et al.: Schweiz. med. Wchnschr. *89*:1126, 1959. 2. Fuchs, M. et al.: Current Therap. Research 2:11, Jan. 1960. 3. Reutter, F. and Schaub, F: Schweiz. med. Wchnschr. *89*:1158, 1959. 4. Veyrat, R. et al.: Schweiz. med. Wchnschr. *89*:1133, 1959. 5. Ford, R. V.: Manuscript submitted for publication. 6. Analysis of Case Reports Compiled by Biostatistical Dept. of Geigy Pharmaceuticals. 7. Bryant, J. M.: Report to Geigy Pharmaceuticals.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.

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Complete information on Elipten is available on request.

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SUPPLIED: *Tablets,* 250 mg. (white, scored); bottles of 100.

1. Forster, F. M.: Wisconsin M. J. *58*:375 (July) 1959. 2. Meyer, J. S.: M. Times *87*:743 (June) 1959. 3. Lambros, V. S.: Dis. Nerv. System *19*:349 (Aug.) 1958. 4. Niswander, G. D., and Karacan, I.: Am. J. Psychiat. *116*:260 (Sept.) 1959. 5. Carter, C. H.: Dis. Nerv. System *21*:50 (Jan.) 1960.

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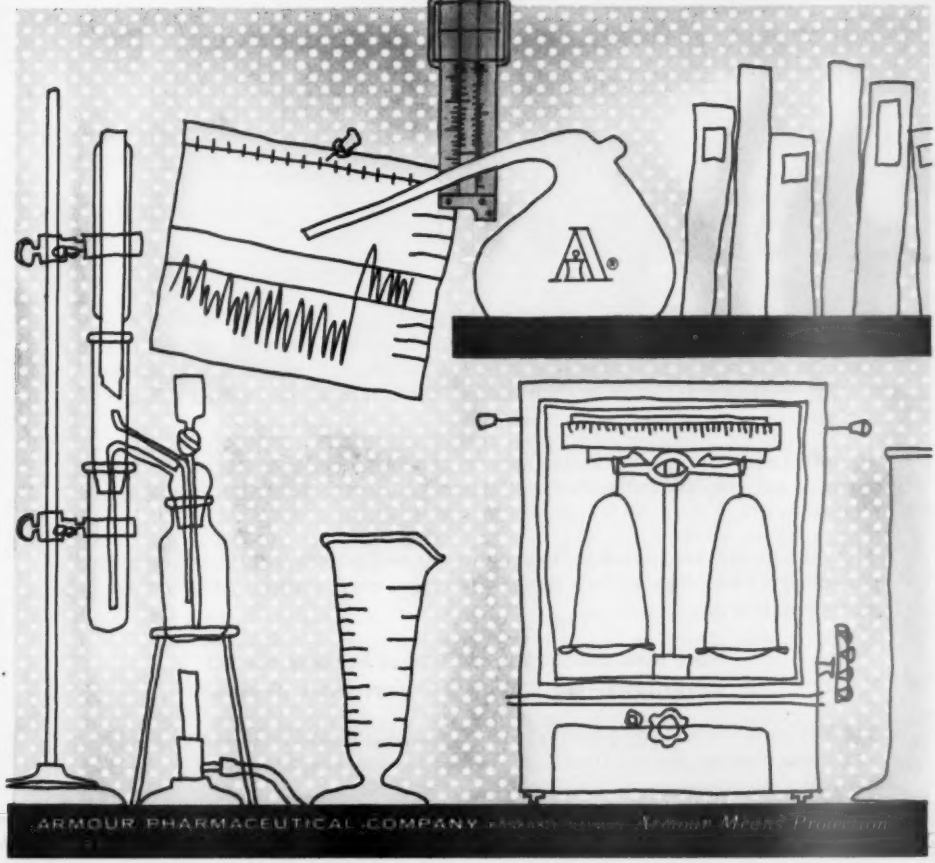

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1. Goddard, E.S.: in *Trifluoperazine, Further Clinical and Laboratory Studies*, Philadelphia, Lea & Febiger, 1959.

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In 8 out of 10 patients complete control of grand mal seizures with

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Results in 262 epileptic patients when "Mysoline" was used alone.

Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%
Grand Mal	214	172 (80%)	15 (7%)	27 (13%)
Psychomotor	29	19 (65%)		10 (35%)
Focal Jacksonian	19	19 (100%)		

Results in 835 epileptic patients who had failed to respond successfully to other anticonvulsants. "Mysoline" was added to current medication which, in some cases, was eventually replaced by "Mysoline" alone.

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Grand Mal	613	175 (28.5%)	253 (41.2%)	185 (30.3%)
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for prompt, prolonged relief of allergic symptoms through inherently sustained action at the cellular level...with b.i.d. dosage

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Tacaryl possesses inherent long-acting properties. After rapid disappearance from the blood serum, Tacaryl is bound to the tissues. This protective affinity for tissue provides a notably sustained effect which does not depend upon the use of artificial, long-acting construction. The sustained action is an inherent property of the molecule and lasts for periods up to 12 hours.

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Tacaryl is absorbed quickly to provide rapid relief of symptoms. This action is due to the rapid transport of Tacaryl from the blood stream to the tissues.

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In studies to date,[1] side effects were minimal; only in a small percentage of cases was mild drowsiness observed. Tolerance was not reported even after long usage. No cumulative effect has been observed.

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In a study of 459 patients[1] Tacaryl provided effective symptomatic relief in a wide variety of conditions including allergic rhinitis, pruritus, various skin disorders, allergic bronchial asthma, pruritus of chickenpox and allergic conjunctivitis. In some cases, the relief of itching bordered on the dramatic.[2] In a double-blind clinical evaluation[3] of various antihistaminic agents in hay fever, Tacaryl provided benefits in all patients with moderate to severe symptoms.

dosage: Adults: *Tablets*—One tablet (8 mg.) twice daily. *Syrup*—Two 5 cc. teaspoonfuls (8 mg.) twice daily. Children: *Tablets*—One-half tablet (4 mg.) twice daily. *Syrup*—One 5 cc. teaspoonful (4 mg.) twice daily.

In some patients it may be desirable to adjust the dosage to meet individual requirements.

supplied: Scored tablets, 8 mg., bottles of 100. Syrup, 4 mg. per 5 cc. tsp., 16 oz. bottles.

references: (1) Clinical Research Division, Mead Johnson & Company. (2) Howell, C. M., Jr.: Evaluation of Methdilazine as an Antipruritic Agent, North Carolina M. J. *21* (May) 1960 (in press). (3) Wahner, H. W., and Peters, C. A.: An Evaluation of Some Newer Antihistaminic Drugs Against Pollinosis, Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960.

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Schedule of Postgraduate Courses, Autumn-Winter, 1960-1961

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	Sept.		Oct.					Nov.				Dec.				Jan.					Feb.		
	19–23	26–30	3–7	10–14	17–21	24–28	Oct. 31–Nov. 4	7–11	14–18	21–25	Nov. 28–Dec. 2	5–9	12–16	19–23	26–30	2–6	9–13	16–20	23–27	Jan. 30–Feb. 3	6–10	13–17	20–24
Course No. 1, THE PLACE OF HEMATOLOGY IN INTERNAL MEDICINE: WITH AN INTRODUCTION TO RADIOISOTOPE TECHNICS AND THEIR APPLICATION: The Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director.	X																			*			
Course No. 2, CANCER AND THE INTERNIST—1960 CONCEPTS: Memorial Center, Sloan-Kettering Institute for Cancer Research, New York, N. Y.; Rulon W. Rawson, M.D., F.A.C.P., Director.				X																			
Course No. 3, ELECTROCARDIOGRAPHY: University of Utah College of Medicine, Salt Lake City, Utah; Hans H. Hecht, M.D., F.A.C.P., Director.								X															
Course No. 4, RECENT ADVANCES IN DRUG THERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.																	X						
Course No. 5, MECHANISMS OF DISEASE: Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors.																		X					
Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE: The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D., (Associate), Associate Director.																							X

The following courses are scheduled for Spring, 1961: CARDIOVASCULAR DISEASES, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director, March 6–10; INTERNAL MEDICINE, McGill University, Ronald V. Christie, M.D., F.A.C.P., Director, March 13–17; ADVANCED CLINICAL ELECTROCARDIOGRAPHY, The University of Tennessee, I. Frank Tullis, M.D., F.A.C.P., Director, March 20–24; ENDOCRINOLOGY, University of Virginia, William Parson, M.D., F.A.C.P., Director, March 23–25; PROBLEMS OF GROWTH AND AGING, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director, April 12–15; GASTROENTEROLOGY, University of Pennsylvania School of Medicine, Henry L. Bockus, M.D., F.A.C.P., Director, May 15–19; CURRENT ASPECTS OF INTERNAL MEDICINE, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director, June 19–23.

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by increasing
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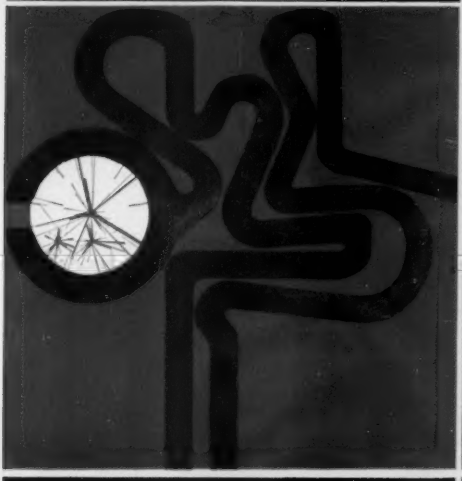

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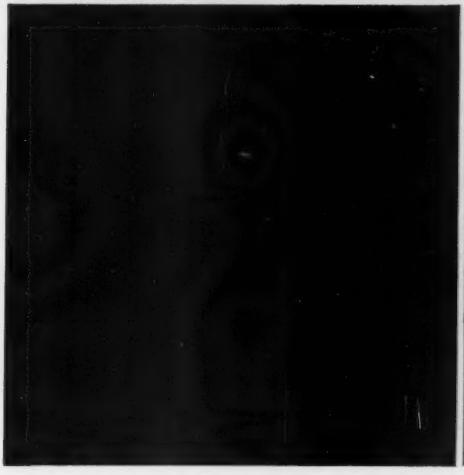

[illegible] Arch. Int. Pharmacodyn. 132, 1958. (2) Kersley, G. D.; Cass, E. P., and Torrie, D. C. J. Ann. Rheumat. Dis. 17:326, 1958. (3) Ogryzlo, M. A., and Harrison, J.: Ann. Rheumat. Dis. 18:425, 1959.

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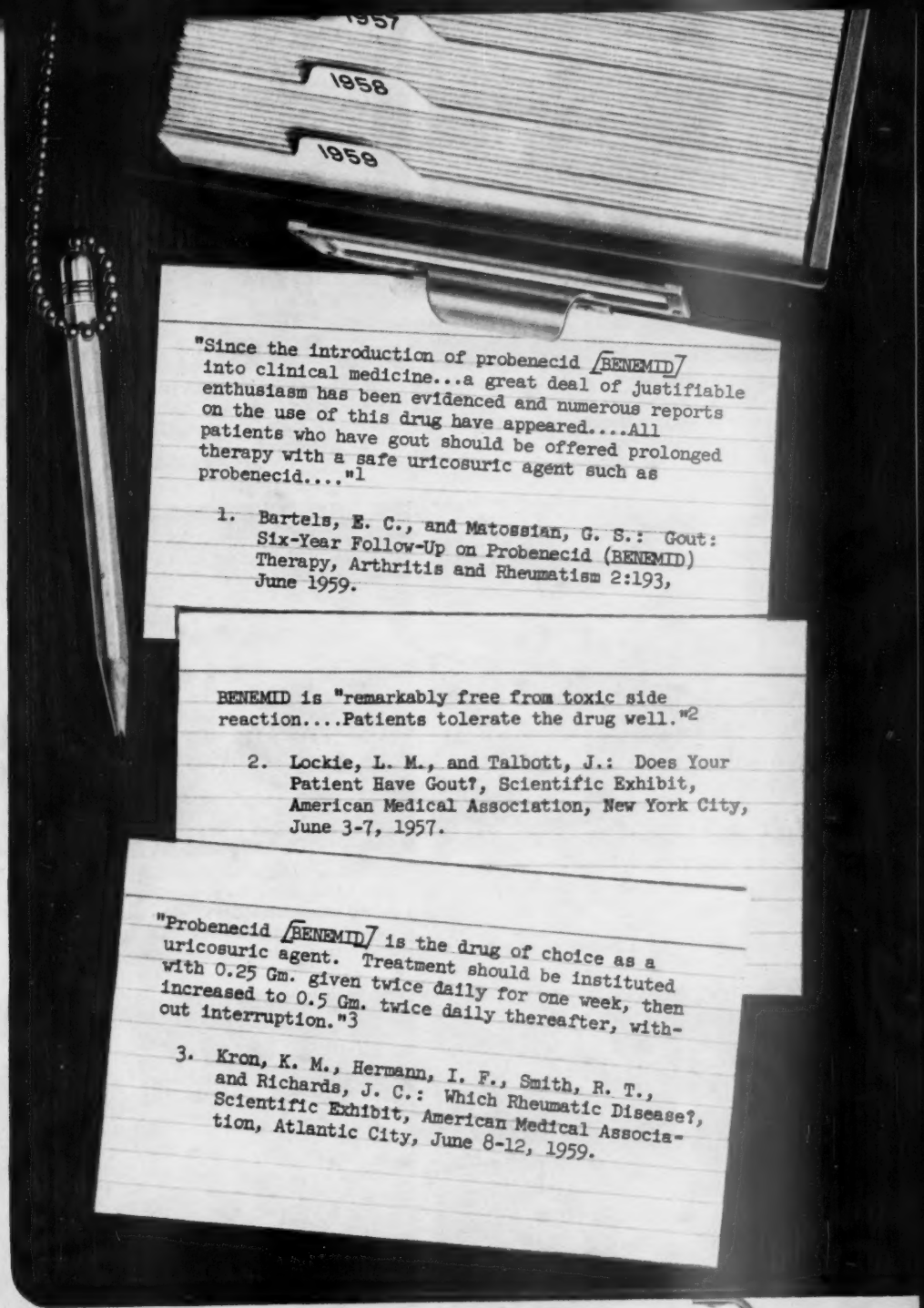

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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

BENEMID is "remarkably free from toxic side reaction....Patients tolerate the drug well."[2]

2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

"Probenecid [BENEMID] is the drug of choice as a uricosuric agent. Treatment should be instituted with 0.25 Gm. given twice daily for one week, then increased to 0.5 Gm. twice daily thereafter, without interruption."[3]

3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

Supply: BENEMID* probenecid, 0.5 Gm. tablets, bottles of 100 and 1000.

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TOTAL	103	79	16	8

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1. Billow, B.W., *et al.*: Southwestern Med. *41*:286, 1960.
2. Teitel, L. H., *et al.*: Indust. Med. *29*:150, (April) 1960.
3. Taub, S. J.: Paper presented before the Annual Meeting, Pi Lambda Kappa Medical Fraternity, Miami, Florida (March) 1960. 4. Clinical Reports to the Medical Dept., Armour Pharmaceutical Co., 1959.

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis.* 8:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics* 14:545 (Sept.) 1959.
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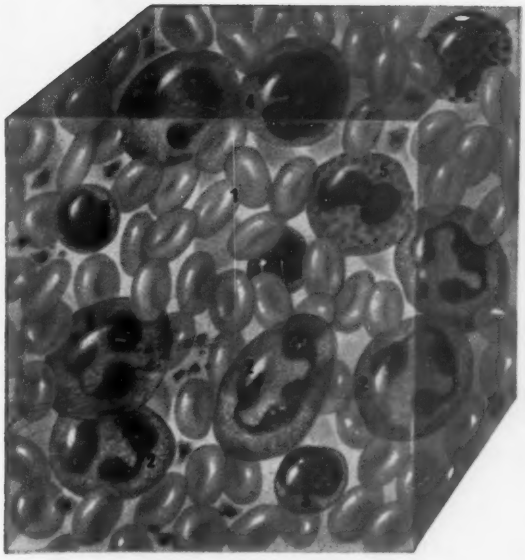

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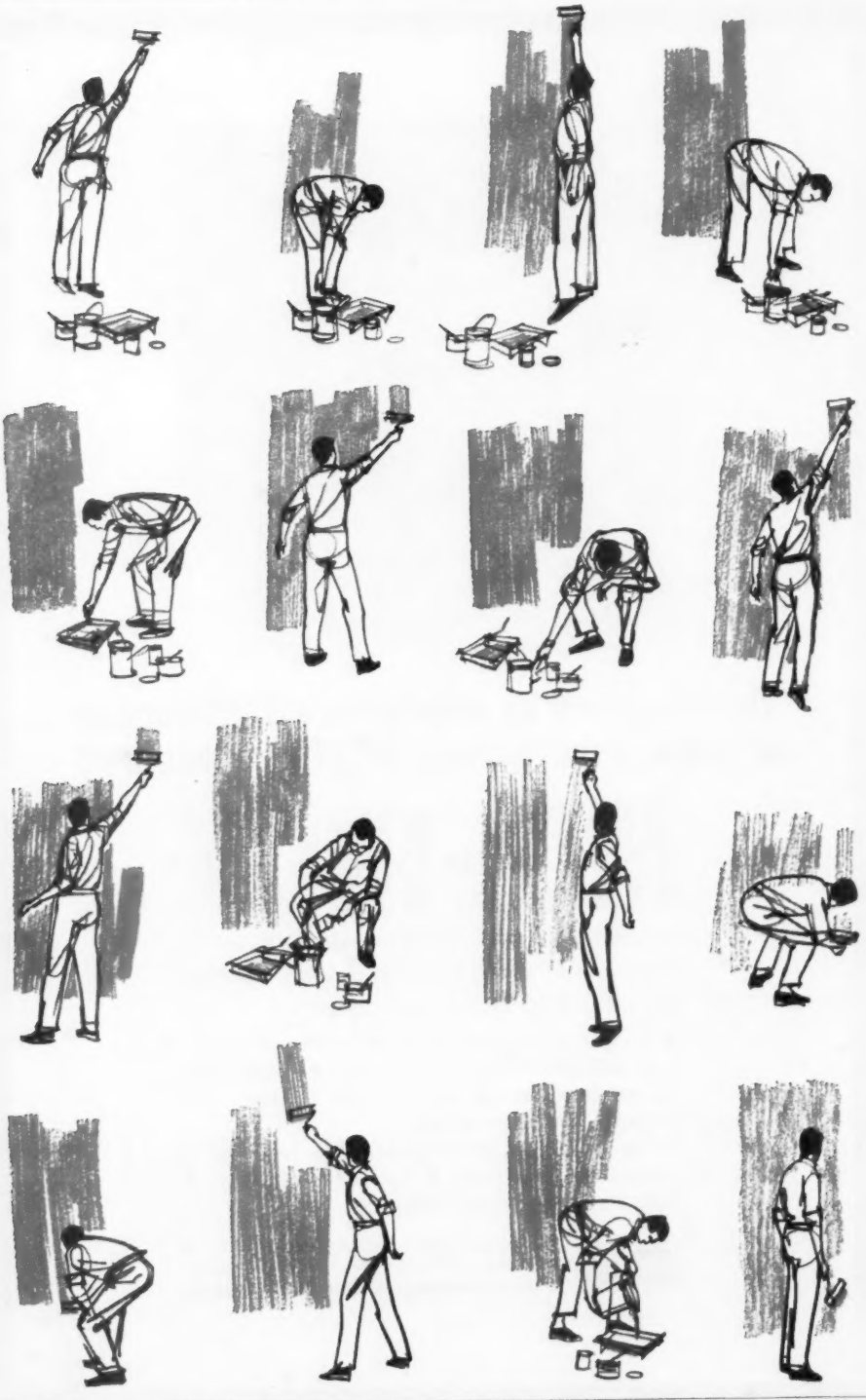

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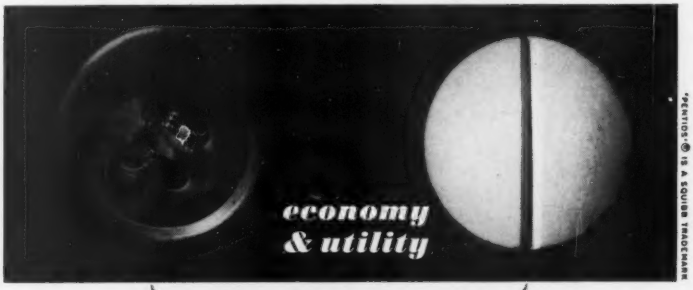

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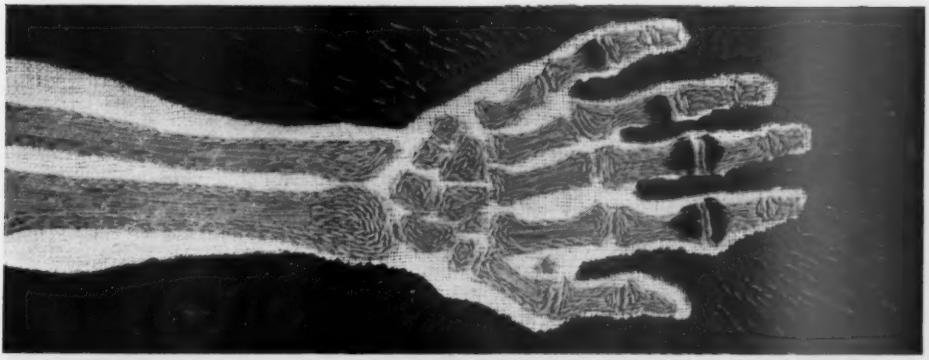

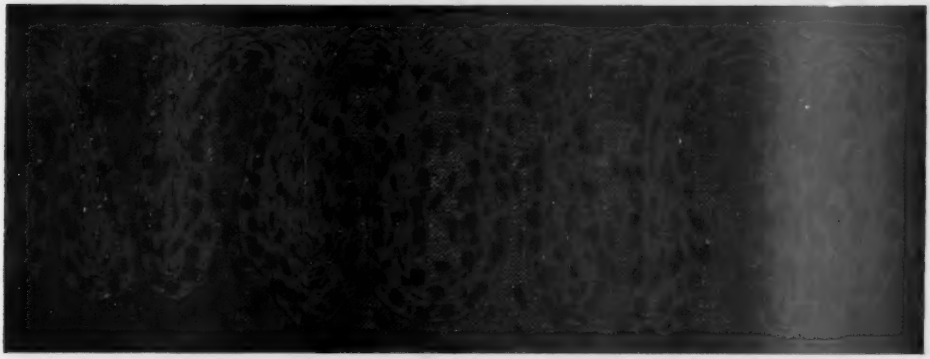

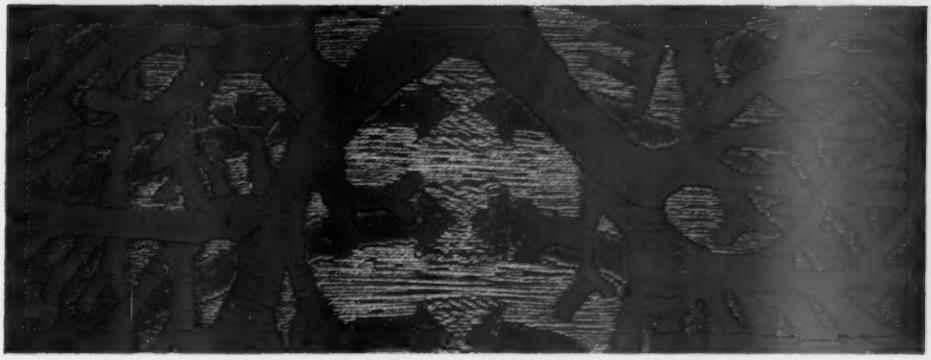

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*Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958.

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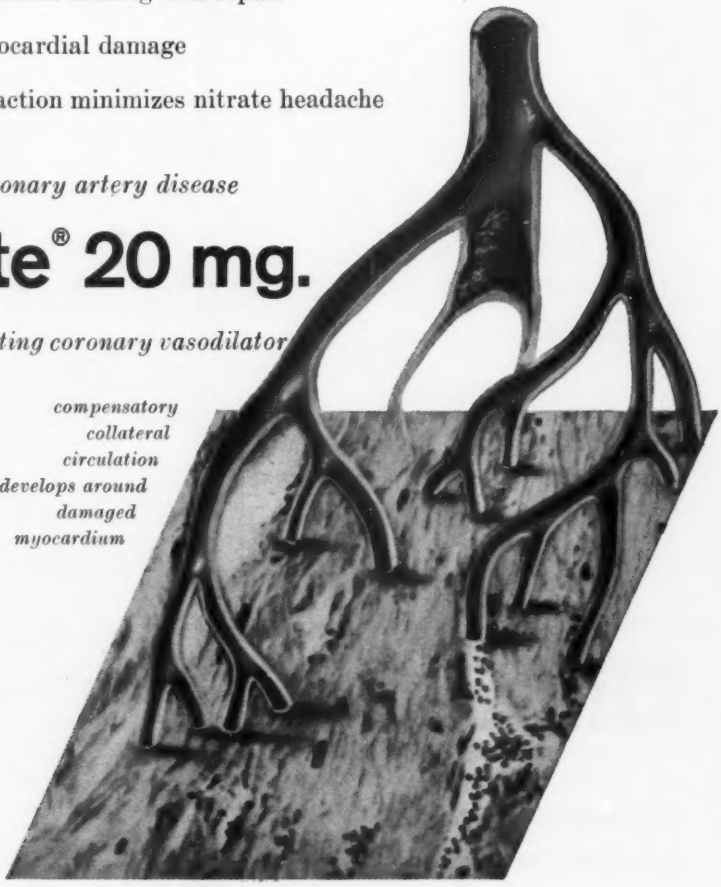

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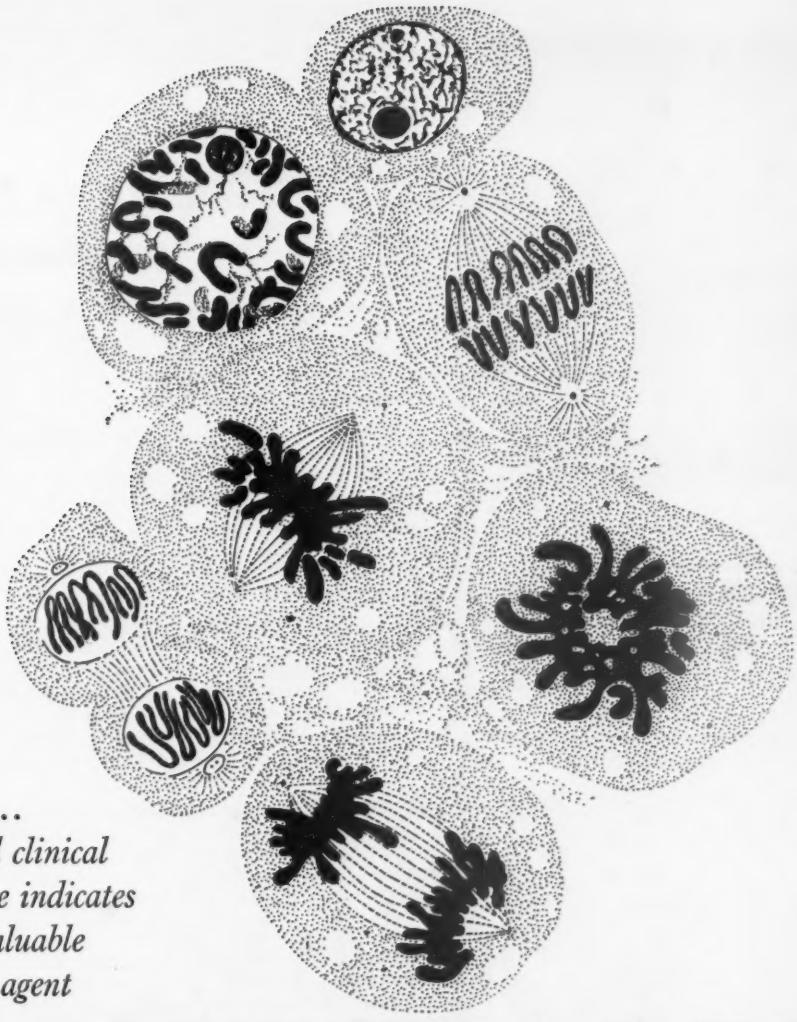

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*Papac, R.; Petrakis, N. L.; Amini, E. and Wood, D. A.: J.A.M.A. *172*:1387-1391 (March 26) 1960.

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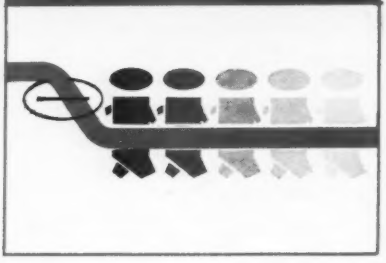

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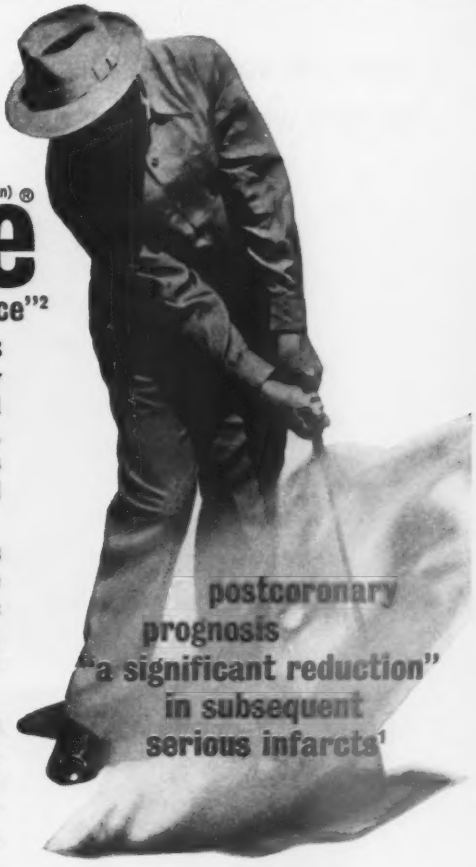

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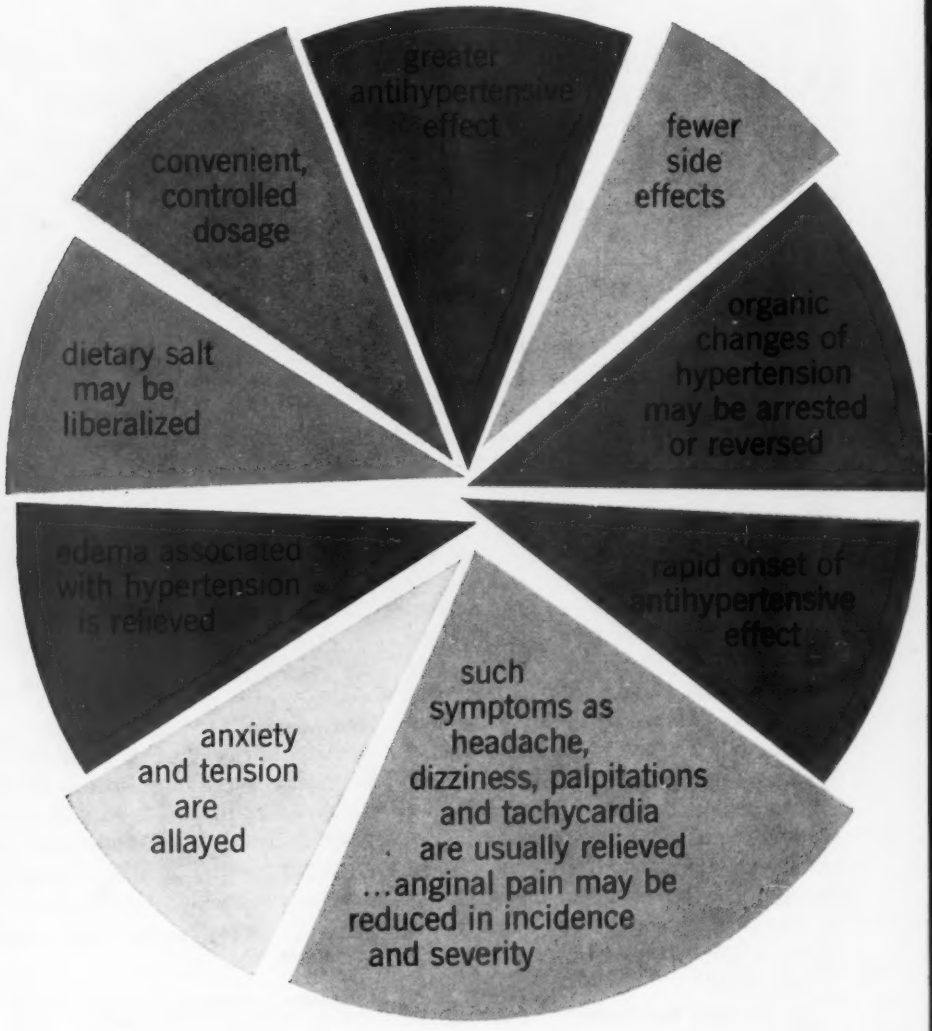
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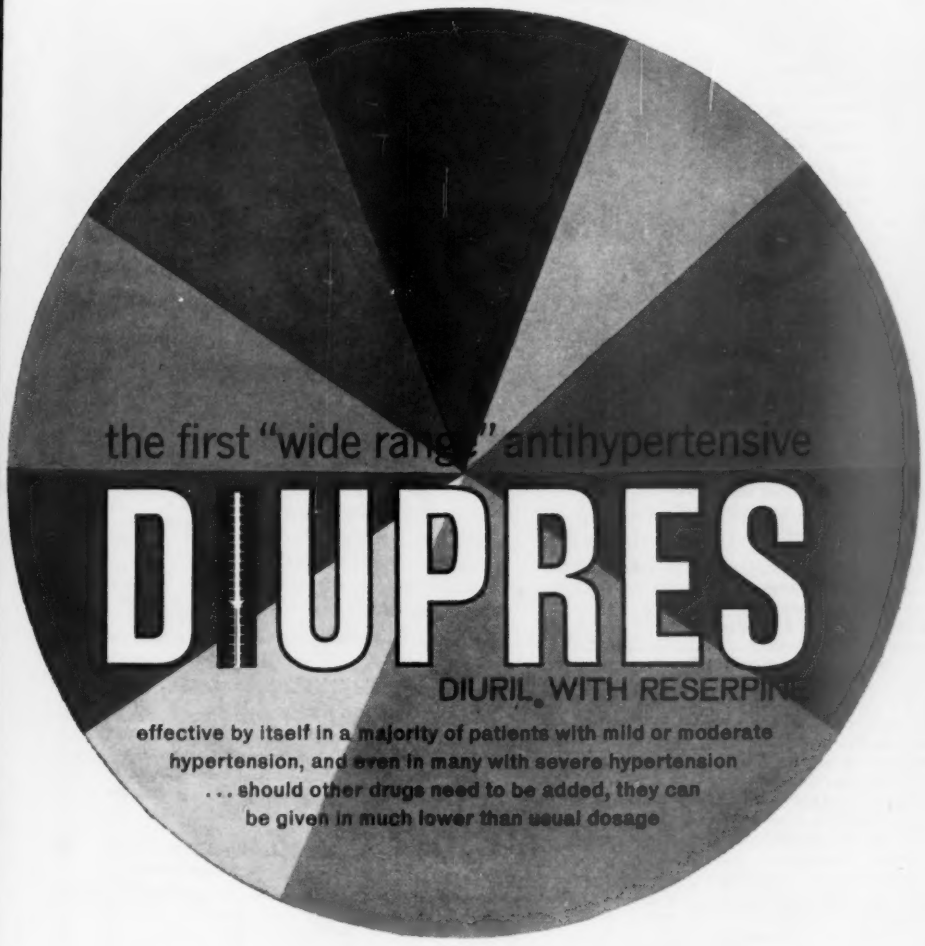
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INDEX TO ADVERTISERS

AUGUST, 1960

Abbott Laboratories 12–13, 25, 27, 29, 31, 136
Adolph's Limited 25
A. C. P. Gifts 98
A. C. P. Postgraduate Courses 116
Ames Company, The 14, 50
A. I. M. Are you moving 27
A. I. M. Subscriptions 74
A. I. M. Wanted Back Issues 67, 128
Armour Pharmaceutical Company 10, 109, 121
Astra Pharmaceutical Products, Inc. 9
Ayerst Laboratories 54, 113
Borcherdt Company 131
Ciba Pharmaceutical Products, Inc. 19, 32, 38, 72–73, 89, 90–91, 92–93, 108, 130, 131
Eaton Laboratories 100
Endo Laboratories 22, 103
E. Fougera & Company, Inc. 65
Geigy Chemical Corporation 6, 46, 55, 71, 106–107, 117
Glenwood Laboratories 141
Hyland Laboratories 58
Irwin Neisler & Company 40–41
Ives-Cameron Company 57
Jesse Jones Volume Files 74
Lederle Laboratories, Div. American Cyanamid Co. 24, 129
Thos. Leeming & Company 2, 43
Eli Lilly & Company ..... Third Cover
Lloyd Brothers, Inc. 88
Macmillan Company, The 1
Maltbie Laboratories 8
McNeil Laboratories, Inc. 51, 101
Mead Johnson & Company 33, 114–115, 133
Merck Sharp & Dohme 4–5, 36–37, 68–69, 80–81, 96, 111, 118–119, 138–139
Wm. S. Merrell Company, The 76–77
Parke, Davis & Company 47
Pfizer Laboratories, Div. Chas. Pfizer Co., Inc. 110, 134
Pharmacia Laboratories 86
Reed & Carnrick 23
Riker Laboratories ..... Second Cover, 79, 142
A. H. Robins Company 7, 82
Roche Laboratories, Div. Hoffmann-LaRoche, Inc. 16–17, 34, 60–61, 122–123, 135
J. B. Roerig & Company 78
Wm. H. Rorer, Inc. 11
Sanborn Company 30
Sandoz Pharmaceuticals ..... Insert facing 32
Schering Corporation 63, 65, 67
Schieffelin & Company 39, 137
G. D. Searle & Company 97
Smith, Kline & French Laboratories 15, 56, 70, 95, 112
E. R. Squibb & Sons, Div. Olin Mathieson Chemical Corp. 18, 29, 42, 75, 128
Tufts University School of Medicine 128
Upjohn Company, The 66, 105
U. S. Vitamin Corporation 44–45
Vaponefrin Company, The 99
Wallace Laboratories 26, 35, 52–53, 84–85, 87, 102, 120, 126–127
Warner-Chilcott Laboratories 3, 48, 49, 83, 94, 124, 132
Warren-Teed Products, Inc. 64
Westwood Pharmaceuticals 104
White Laboratories, Inc. 28, 125
Winthrop Laboratories, Inc. 62
Woodward Medical Personnel Bureau 67
Wyeth Laboratories 20–21
Wynn Pharmacal Corporation 59

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1. Cohen, R. V., Lambert, R. L., and Molthan, L.: The Use of POTABA in Sarcoidosis; Annual Meeting American Trudeau Society, Eastern Section, Boston, Mass. (1958).

2. Zarafonetis, C. J. D., and Horrax, T. M.: Treatment of Peyronie's Disease with POTABA, Journal of Urology, 81: 770-772 (June 1959).

POTABA DOSAGE FORMS

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2 Gram sealed **ENVELOPES** (50's)

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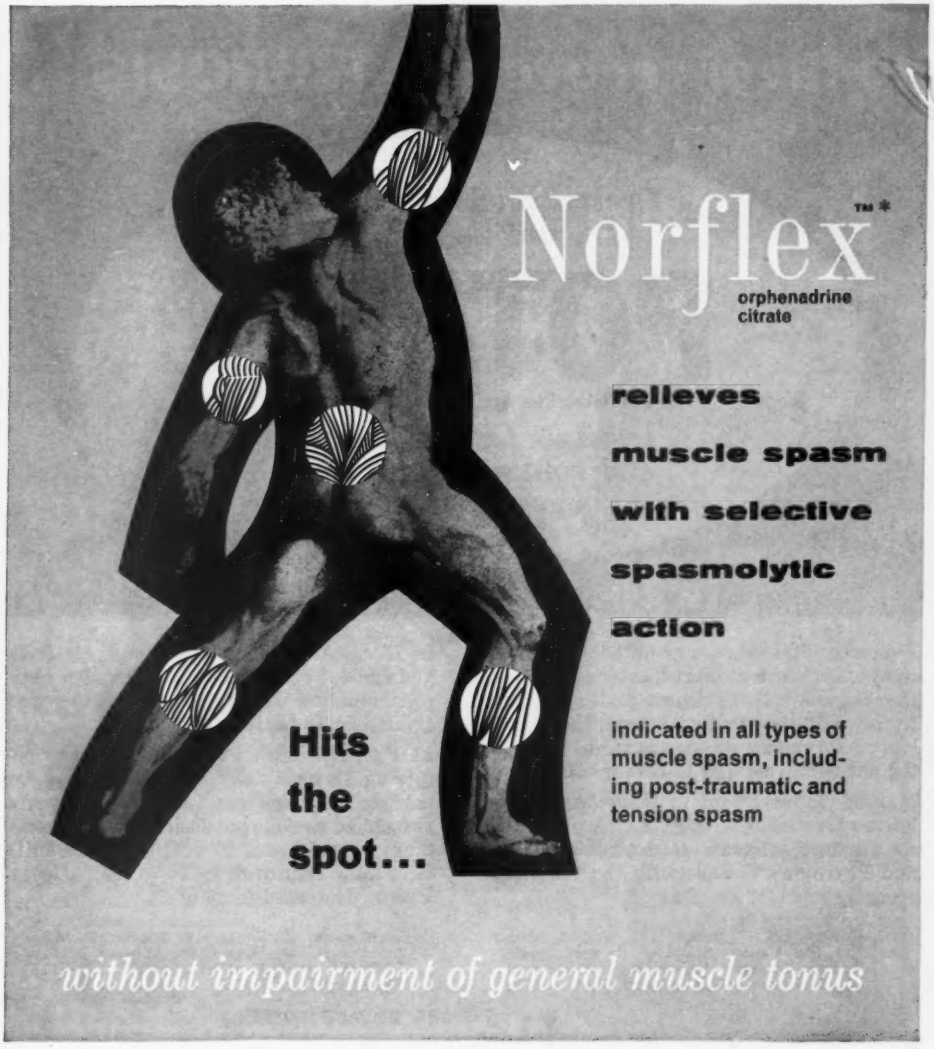
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